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Last logoff:  16may08 13:35:55
Logon file405 27may08 12:36:48
               *** ANNOUNCEMENTS ***
                      ***
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***The 2008 EMTREE Thesaurus has been added to EMBASE (Files 72, 73,
772, and 972)***

RESUMED UPDATING
***File 120, U.S. Copyrights
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RELOADS COMPLETED
***File 156, ToxFile (annual reload)
***Files 154 & 155, MEDLINE (annual reload)
***Files 72 & 73, EMBASE
                      ***
FILES REMOVED
***Files 476/Financial Times & 473/Financial Times Abstracts
***Files 359, 959, 804, Chemical Economics Handbook
***Files 360, 960, Specialty Chemicals Update Program
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SYSTEM HOME
Cost is in DialUnits
Menu System II:  D2 version 1.8.0 term=ASCII
                    *** DIALOG HOMEBASE(SM) Main Menu ***

 Information:
   1.   Announcements (new files, reloads, etc.)
   2.   Database, Rates, & Command Descriptions
   3.   Help in Choosing Databases for Your Topic
   4.   Customer Services (telephone assistance, training, seminars, etc.)
   5.   Product Descriptions

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   6.   DIALOG(R) Document Delivery
   7.   Data Star(R)

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       /H = Help              /L = Logoff            /NOMENU = Command Mode


Enter an option number to view information or to connect to an online
 service.  Enter a BEGIN command plus a file number to search a database
(e.g., B1 for ERIC).
? b 410

        27may08 12:36:48 User217743 Session D729.1
              $0.00      0.271 DialUnits FileHomeBase
       $0.00   Estimated cost FileHomeBase
       $0.00   Estimated cost this search
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      $0.00   Estimated total session cost    0.271 DialUnits

File 410:Dialog Comm-of-Interest Newsletters 2008/Mar
       (c) 2008 Dialog

      Set   Items   Description
      ---   -----   -----------
? set hi ;set hl
HILIGHT set on as ''
HILIGHT set on as ''
? b 155
       27may08 12:37:03 User217743 Session D729.2
            $0.00      0.117 DialUnits File410
      $0.00   Estimated cost File410
      $0.06   TELNET
      $0.06   Estimated cost this search
      $0.06   Estimated total session cost    0.388 DialUnits

File 155:MEDLINE(R) 1950-2008/May 26
       (c) format only 2008 Dialog
*File 155: MEDLINE has reloaded. Please see HELP NEWS 155
for details.

      Set   Items   Description
      ---   -----   -----------
? s infertility and (administer or administration) and (fsh or lh or hcg)
          48698   INFERTILITY
           8361   ADMINISTER
        1530960   ADMINISTRATION
          24899   FSH
          39216   LH
          17552   HCG
      S1    1146   INFERTILITY AND (ADMINISTER OR ADMINISTRATION) AND (FSH
                   OR LH OR HCG)
? s s1 and py>1998
           1146   S1
        5491440   PY>1998
      S2     496   S1 AND PY>1998
? s s1 not s2
           1146   S1
            496   S2
      S3     650   S1 NOT S2
? s s3 and ti=infertility
>>>Prefix "TI" is undefined
            650   S3
              0   TI=INFERTILITY
      S4      0   S3 AND TI=INFERTILITY
? s s3 and infertility/ti
            650   S3
           8130   INFERTILITY/TI
      S5     69   S3 AND INFERTILITY/TI
? s s5 and (fsh or lh or hcg)/ti
             69   S5
           3989   FSH/TI
           7458   LH/TI
           3078   HCG/TI
      S6     10   S5 AND (FSH OR LH OR HCG)/TI
? t s6/3,ab,kwic/1

 6/3,AB,KWIC/1
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

11876611    PMID: 8796182
   [Value of high-dose pure FSH in the treatment of idiopathic male
infertility]
   Interet de la FSH pure a forte dose dans le traitement de
l'infertilite masculine idiopathique.
   Iacono F; Barra S; Montano L; Lotti T
   Clinique Urologique, Faculte de Medecine de Catanzaro, Universite de
Reggio Calabre, Naples, Italie.
   Journal d'urologie (FRANCE)    1996, 102 (2) p81-4, ISSN 0248-0018--
Print   Journal Code: 8006503
   Publishing Model: Print
   Document type: Clinical Trial; Controlled Clinical Trial; English
Abstract; Journal Article; Randomized Controlled Trial
   Languages: FRENCH
   Main Citation Owner: NLM
   Record type: MEDLINE; Completed
   Several, more or less successful, medical treatments have been proposed
for idiopathic male infertility. We assessed the effect of high-dose
FSH (150 IU) in patients with idiopathic oligosperma in comparison
with patients given low doses. In the high-dose group, there was a
significant rise in spermatozoid concentration (p < 0.0001), mobility (p <
0.0001) and morphology (p < 0.007).
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[Value of high-dose pure FSH in the treatment of idiopathic male infertility]
Interet de la FSH pure a forte dose dans le traitement de l'infertilite masculine idiopathique.
Several, more or less successful, medical treatments have been proposed for idiopathic male infertility. We assessed the effect of high-dose FSH (150 IU) in patients with idiopathic oligospermia in comparison with patients given low doses. In...
Descriptors: *Follicle Stimulating Hormone--administration and dosage--AD; *Infertility, Male--drug therapy--DT; *Oligospermia--drug therapy--DT

6/3,AB,KWC/2
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

10907028 PMID: 8147183
[What advantages does treatment with highly purified FSH have in infertility?]
Welche Vorteile bringt eine Behandlung mit hochgereinigtem FSH bei unerfulltem Kinderwunsch?
Breckwoldt M, Nieschlag E, Runnebaum B, Schneider H P
Zentrum fur Frauenheilkunde, Westfalische Wilhelms-Universitat, Munster, Bundesrepublik Deutschland.
Zentralblatt fur Gynakologie (GERMANY) 1994, 116 (1) p56-7, ISSN 0044-4197--Print Journal Code: 21820100R
Publishing Model: Print
Document type: Consensus Development Conference; Journal Article; Review
Languages: GERMAN
Main Citation Owner: NLM
Record type: MEDLINE; Completed

[What advantages does treatment with highly purified FSH have in infertility?]
Welche Vorteile bringt eine Behandlung mit hochgereinigtem FSH bei unerfulltem Kinderwunsch?
Descriptors: *Follicle Stimulating Hormone--administration and dosage--AD; *Infertility, Female--therapy--TH; Fertilization in Vitro; Humans; Infant, Newborn; Infertility, Female--etiology--ET; Luteinizing Hormone--blood--BL; Ovulation Induction; Pregnancy

6/3,AB,KWC/3
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

09272025 PMID: 2485730
Treatment of infertility of hypothalamic origin in women by means of pulsatile LH-RH administration.
Grabinski M, Bolanowski M, Zalewski J, Mlewicz A
Endokrynologia Polska (POLAND) 1989, 40 (6) p285-9, ISSN 0423-104X --Print Journal Code: 0370674
Publishing Model: Print
Document type: Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Treatment of infertility of hypothalamic origin in women by means of pulsatile LH-RH administration.
Descriptors: *Gonadotropin-Releasing Hormone--administration and dosage--AD; *Hypothalamic Diseases--complications--CO; *Infertility, Female--drug therapy--DT; Adult; Gonadotropin-Releasing Hormone--deficiency --DF; Hormones--administration and dosage--AD; Humans; Infertility, Female--etiology--ET; Infusion Pumps; Infusions, Intravenous--instrumentation--IS; Infusions, Intravenous--methods--MT

6/3,AB,KWC/4
DIALOG(R)File 155:MEDLINE(R)
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08270832 PMID: 3556332
[Successful treatment of female infertility of hypothalamic origin using pulsed administration of gonadotropin-releasing hormone (LHRH)]
Skuteczne leczenie niepodnosci kobiecej pochodzenia podwzgorzowego za pomoca pulsacyjnego podawania hormonu uwalniajacego gonadotropiny (LH -RH).
Grabinski M, Bolanowski M, Zalewski J, Zbrog U
Ginekologia polska (POLAND) Jan 1987, 58 (1) p11-6, ISSN 0017-0011 --Print Journal Code: 0374641
Publishing Model: Print
Document type: Case Reports; English Abstract; Journal Article

Languages: POLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

[Successful treatment of female infertility of hypothalamic origin using pulsed administration of gonadotropin-releasing hormone (LHRH)]
Skuteczne leczenie niepłodności kobiecej pochodzenia podwzgorzowego za pomoca pulsacyjnego podawania hormonu uwalniajacego gonadotropiny (LH-RH).
Descriptors: *Gonadotropin-Releasing Hormone--administration and dosage--AD; *Infertility, Female--drug therapy--DT; Adult; Humans; Infertility, Female--etiology--ET; Infusions, Intravenous

6/3,AB,KW C/5
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

08177017 PMID: 3099447
HCG and HMG treatment of male infertility with pituitary problems.
Usui T; Ishibe T; Matsumoto S
Urology (UNITED STATES) Jan 1987, 29 (1) p50-3, ISSN 0090-4295--Print Journal Code: 0366151
Publishing Model: Print
Document type: Case Reports; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
A case is presented of a twenty-nine-year-old acromegalic man with sexual problems and fertility disturbance due to pituitary adenoma, who successfully fathered. Various endocrinologic studies, skill x-ray film and computerized tomography (CT) scan revealed a pituitary adenoma. Testicular biopsy specimen also supported that the cause of sexual problems and fertility disturbance was secondary in origin. One month after transsphenoidal pituitary adenectomy, administration of human chorionic gonadotropin and human menopausal gonadotropin was started. His potency was improved immediately after start of the treatment, and his wife became pregnant five months later.
HCG and HMG treatment of male infertility with pituitary problems.
...sexual problems and fertility disturbance was secondary in origin. One month after transsphenoidal pituitary adenectomy, administration of human chorionic gonadotropin and human menopausal gonadotropin was started. His potency was improved immediately...
Descriptors: *Adenoma--complications--CO, *Chorionic Gonadotropin--therapeutic use--TU; *Infertility, Male--drug therapy--DT; *Menotropins--therapeutic use--TU; *Pituitary Neoplasms--complications--CO; Acromegaly--etiology--ET; Adult; Humans; Infertility, Male--etiology--ET

6/3,AB,KW C/6
DIALOG(R)File 155:MEDLINE(R)
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07954850 PMID: 3086957
[A new therapeutic approach to infertility in polycystic ovaries: pure FSH].
Une nouvelle approche therapeutique de la sterilite dans les ovaires polykystiques: la FSH pure.
Draper-Faure E
Revue francaise de gynecologie et d'obstetrique (FRANCE) Apr 1986, 81 (4) p179-84, ISSN 0035-290X--Print Journal Code: 0411346
Publishing Model: Print
Document type: English Abstract; Journal Article
Languages: FRENCH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Current improved understanding of the physiopathology of polycystic ovary syndrome offers the possibility of more suitable treatment. Formerly, objectives differed for a given patient: re-establish regular cycles using progestogens or estroprogestogens, reduce hirsutism with antiandrogens, trigger ovulation. Clomid is the inducer of choice, but setbacks occur. Injectable gonadotropins were, in principle, a contraindication due to the high incidence of excess stimulation and multiple pregnancy. The introduction of purified FSH offers another method of stimulation. Severe excess stimulation is eliminated with a suitable protocol involving administration of small doses. This offers hope, but as yet no large-scale trial has been published.

[A new therapeutic approach to infertility in polycystic ovaries: pure FSH].
Une nouvelle approche therapeutique de la sterilite dans les ovaires polykystiques: la FSH pure.

... due to the high incidence of excess stimulation and multiple pregnancy. The introduction of purified FSH offers another method of stimulation. Severe excess stimulation is eliminated with a suitable protocol involving administration of small doses. This offers hope, but as yet no large-scale trial has been...
Descriptors: *Follicle Stimulating Hormone--therapeutic use--TU; *Infertility, Female--drug therapy--DT; *Polycystic Ovary Syndrome--complications--CO

6/3,AB,KWC/7
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

05158652 PMID: 783018
[Effect of short-term administration of LH-HR in male infertility on hormonal and seminal parameters]
Wplyw krotkotrwalego stosowania LH-RH na niektore parametry endokrynologiczne i seminologiczne w przypradkach ograniczonej plodnosci u mezczyzn
Fraioli F; Dondero F
Ginekologia polska (POLAND) 1976, 47 (6) p655-62, ISSN 0017-0011--Print Journal Code: 0374641
Publishing Model: Print
Document type: English Abstract; Journal Article
Languages: POLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

[Effect of short-term administration of LH-HR in male infertility on hormonal and seminal parameters]
Wplyw krotkotrwalego stosowania LH-RH na niektore parametry endokrynologiczne i seminologiczne w przypradkach ograniczonej plodnosci u mezczyzn

6/3,AB,KWC/8
DIALOG(R)File 155:MEDLINE(R)
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05012192 PMID: 766699
[Male hypogonadotrophic hypogonadism successful treatment of infertility with HMG + HCG (author's transl)]
Hypogonadisme hypogonadotrope masculin: succes du traitement de la sterilite par H.M.G. + H.C.G.
Gayral M.N.; Millet D.; Mandelbaum J.; Serfaty D.; Netter A.
Annales d'endocrinologie (FRANCE) Sep-Oct 1975, 36 (5) p227-41, ISSN 0003-4266--Print Journal Code: 0116744
Publishing Model: Print
Document type: Case Reports; English Abstract; Journal Article
Languages: FRENCH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Ten typical cases of male eunuchoidism (two with anosmia) are reported. After administration of clomifene citrate to five patients there was no change in blood levels of gonadotrophins in four cases; in the fifth, a small and transitory increase of LH was noted. The intravenous injection of LHRH (100 mcg) to five patients induced an increase of serum LH in all cases and serum FSH in three cases. The initial site of the dysfunction is possibly hypothalamic with secondary gonadotrophic pituitary insufficiency. Among six patients desiring paternity, prolonged treatment (for 36 to 98 weeks), with HCG (1700-7000 I.U. weekly) + HMG (450-825 I.U. FSG weekly) resulted in the appearance of spermatozoa in the seminal fluid in five cases and a pregnancy was obtained in four cases. Methods of treatment are discussed.

[Male hypogonadotrophic hypogonadism successful treatment of infertility with HMG + HCG (author's transl)]
Ten typical cases of male eunuchoidism (two with anosmia) are reported. After administration of clomifene citrate to five patients there was no change in blood levels of gonadotrophins in four cases; in the fifth, a small and transitory increase of LH was noted. The intravenous injection of LHRH (100 mcg) to five patients induced an increase of serum LH in all cases and serum FSH in three cases. The initial site of the dysfunction is possibly hypothalamic with secondary gonadotrophic pituitary insufficiency. Among six patients desiring paternity, prolonged treatment (for 36 to 98 weeks), with HCG (1700-7000 I.U. weekly) + HMG (450-825 I.U. FSG weekly) resulted in the...

6/3,AB,KWC/9
DIALOG(R)File 155:MEDLINE(R)
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04612184 PMID: 4363158

Long-term therapy with low-dose cisclomphene in male infertility: effects on semen, serum FSH, LH, testosterone ond estradiol, and carbohydrate tolerance.
Reyes F I; Faiman C
International journal of fertility (SWEDEN) 1974, 19 (1) p49-55, ISSN 0020-725X--Print Journal Code: 0374717
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Long-term therapy with low-dose cisclomphene in male infertility: effects on semen, serum FSH, LH, testosterone ond estradiol, and carbohydrate tolerance.
Descriptors: *Carbohydrate Metabolism; *Estradiol--blood--BL; *Follicle Stimulating Hormone--blood--BL; *Infertility, Male--drug therapy--DT; *Luteinizing Hormone--blood--BL; *Semen--drug effects--DE; *Testosterone --blood--BL; Cell Movement; Clomphene--administration and dosage--AD; Clomphene--pharmacology--PD; Clomphene--therapeutic use--TU; Glucose Tolerance Test; Humans; Insulin...

6/3,AB,KWC/10
DIALOG(R)File 155:MEDLINE(R)
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04408913 PMID: 4575636
Therapeutic effect of synthetic luteinizing hormone-releasing hormone (LH-RH) in male infertility due to idiopathic azoospermia and oligospermia.
Zarate A; Valdes-Vallina F; Gonzalez A; Perez-Ubierna C; Canales E S; Schally A V
Fertility and sterility (UNITED STATES) Jun 1973, 24 (6) p485-6, ISSN 0015-0282--Print Journal Code: 0372772
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Therapeutic effect of synthetic luteinizing hormone-releasing hormone (LH-RH) in male infertility due to idiopathic azoospermia and oligospermia.
Descriptors: *Infertility, Male--drug therapy--DT; *Luteinizing Hormone--therapeutic use--TU; *Pituitary Hormone-Releasing Hormones --therapeutic use...
; Adult; Biopsy; Cell Count; Gonadotropins--urine--UR; Humans; Infertility, Male--pathology--PA; Injections, Intramuscular; Leydig Cells; Mitosis; Pituitary Hormone-Releasing Hormones--administration and dosage--AD; Seminal Vesicles--abnormalities--AB; Spermatozoa--drug effects--DE; Testis--pathology--PA
? ds

Set Items Description
S1 1146 INFERTILITY AND (ADMINISTER OR ADMINISTRATION) AND (FSH OR LH OR HCG)
S2 496 S1 AND PY>1998
S3 650 S1 NOT S2
S4 0 S3 AND TI=INFERTILITY
S5 69 S3 AND INFERTILITY/TI
S6 10 S5 AND (FSH OR LH OR HCG)/TI
? s s3 and female()infertility
650 S3
4911582 FEMALE
48698 INFERTILITY
946 FEMALE(W)INFERTILITY
S7 7 S3 AND FEMALE()INFERTILITY
? t s7/3,ab/all

7/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
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12253097 PMID: 9176463
A prospective randomized comparison between long and discontinuous-long protocols of gonadotropin-releasing hormone agonist for in vitro fertilization.
Fujii S; Sagara M; Kudo H; Kagiya A; Sato S; Saito Y
Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, Aomori, Japan.
Fertility and sterility (UNITED STATES) Jun 1997, 67 (6) p1166-8, ISSN 0015-0282--Print Journal Code: 0372772
Publishing Model: Print
Document type: Clinical Trial; Comparative Study; Journal Article;

Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: To investigate the efficacy of a discontinuous-long protocol in an IVF program. DESIGN: Prospective randomized study. SETTING: University hospital. PATIENT(S): One hundred thirty-seven IVF cycles of 92 patients in an outpatient IVF program from April 1995 to December 1995. INTERVENTION(S): In the discontinuous-long protocol group (n = 68), GnRH agonist (GnRH-a) was administered from the luteal phase until cycle day 7, when pure FSH administration was begun. In the long protocol group (n = 69), GnRH-a was administered until the day before hCG administration. MAIN OUTCOME MEASURE(S): Serum LH and ovarian steroid hormone levels, and IVF outcome. RESULT(S): The period and the total dosage of hMG were increased in the discontinuous-long protocol group. Although the fertilization rate was similar under both protocols, the number of embryos transferred was smaller and the cancellation rate was higher in the discontinuous-long protocol group because of the greater failure of oocyte retrieval and fertilization. Serum E2 levels in the late follicular phase were lower in the discontinuous-long protocol group. CONCLUSION(S): Early discontinuation of GnRH-a is not beneficial because of its adverse effects on follicular development.

7/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
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11826900 PMID: 8671501
Endometrial thickness as a predictor of pregnancy after in-vitro fertilization but not after intracytoplasmic sperm injection.
Rinaldi L; Lisi F; Floccari A; Lisi R; Pepe G; Fishel S.
Biogenesi, Servizio di Fisiopatologia della Riproduzione, Casa di Cura Villa Europa, 27 Via Eufrate, 00144 Roma, Italy.
Human reproduction (Oxford, England) (ENGLAND) Jul 1996, 11 (7) p1538-41, ISSN 0268-1161--Print Journal Code: 8701199
Publishing Model: Print
Document type: Comparative Study; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
An ultrasonographic evaluation of the endometrium was performed in 158 patients undergoing ovarian stimulation for an in-vitro assisted reproduction programme. Endometrial thickness was evaluated in 109 patients undergoing in-vitro fertilization (IVF) for female indications and in 49 patients undergoing intracytoplasmic sperm injection (ICSI) for male indications. The maximal endometrial thickness was measured on the day of human chorionic gonadotrophin (HCG) administration by longitudinal scanning of the uterus on the frozen image using electronic callipers placed at the junction of the endometrium-myometrium interface at the level of the fundus. Cases in which the endometrial thickness was >/=10 mm were included in group A; cases in which the endometrial thickness was <10 mm were assigned to group B. The age of the patients, serum 17-beta oestradiol concentrations on the day of HCG administration, the length of follicular stimulation, the number of follicles, 17-beta oestradiol concentrations per follicle on the day of HCG and the number of embryos transferred were analysed in each case. When comparing endometrial thickness and results in IVF and ICSI patients, an endometrium <10 mm predominated in IVF patients (27.5%) compared with those undergoing ICSI (16.7%) (P = 0.05); conversely an endometrium >=10 mm was more frequent in ICSI than in IVF patients. The incidence of pregnancy was higher in IVF group A patients (32/79; 41%) than in IVF group B patients (5/30; 17%) (P = 0.03), whereas no significant difference was found between ICSI group A (13/42; 31%) and ICSI group B (3/7; 43%) patients. Thus, a higher percentage of IVF patients had thin endometrium when compared with ICSI patients; thin endometrium was a prognostic indicator of pregnancy only in the case of a female indication for infertility (IVF). A thin endometrium in cases of female infertility may reflect a previous or present uterine pathology, whereas in indications of male infertility (i.e. cases using ICSI), in the absence of any associated uterine pathology, the presence of a thin endometrium is not predictive.

7/3,AB/3
DIALOG(R)File 155:MEDLINE(R)
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11772875 PMID: 8777340
Early timed follicular aspiration prevents severe ovarian hyperstimulation syndrome.
Tomazevic T; Meden-Vrtovec H.
Department of Obstetrics and Gynecology, University Medical Centre Ljubljana, Slovenia.
Journal of assisted reproduction and genetics (UNITED STATES) Apr 1996, 13 (4) p282-6, ISSN 1058-0468--Print Journal Code: 9206495

Publishing Model: Print
Document type: Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
PURPOSE: Early timed follicular aspiration (ETFA) of one ovary 10-12 hr after administration of chorionic gonadotropin (hCG) is an attempt to prevent severe ovarian hyperstimulation syndrome (OHSS). After the introduction of early timed follicular aspiration ETFA of one ovary in IVF/ET cycles at high risk for severe OHSS, no cases of severe OHSS were registered in the Ljubljana IVF/ET program. In the period before preventive ETFA (1984-1992), there were 16 cases of severe OHSS of 4798 IVF/ET cycles followed by 577 clinical pregnancies. After the introduction of ETFA (1992-1993) there were no cases of severe OHSS of 2289 IVF/ET cycles followed by 364 clinical pregnancies. METHODS: We attempted to evaluate the significance of this observation by comparing two groups of female infertility IVF/ET cycles at high risk for severe OHSS. The occurrence of severe OHSS and clinical parameters in the two groups of IVF/ET cycles at high risk for severe OHSS were compared. RESULTS: In the group of 108 IVF/ET female infertility cycles at high risk of severe OHSS with preventive ETFA, there were no cases of severe OHSS. In the control group of 92 IVF/ET female infertility cycles at high risk for severe OHSS with normally timed follicular aspiration (NTFA) of both ovaries, severe OHSS occurred in 16 cases. The difference in the occurrence of severe OHSS between the two groups is highly significant (P < 0.005), both in hMG/hCG- and in GnRHa/hMG/hCG-induced IVF/ET cycles. No difference in live birth rate (16 vs. 16%) between the two groups was noted. CONCLUSIONS: Considering these results we conclude that ETFA is another successful option to decrease the incidence of severe OHSS in assisted reproduction. The preventive effect of follicular aspiration seems to depend on its timing.

7/3,AB/4
DIALOG(R)File 155:MEDLINE(R)
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11003937 PMID: 8036387
[Treatment of female infertility due to hyperandrogenism]
Traitement des infertilites feminines par hyperandrogenie.
Cordray J P; Siboulet B; Marceron R E; Guillerd X; Nys P
Service d'Endocrinologie, Diabetologie, Nutrition, Hopital Notre-Dame de Bon Secours, Paris.
Revue francaise de gynecologie et d'obstetrique (FRANCE) May 1994, 89 (5) p255-66, ISSN 0035-290X--Print Journal Code: 0411346
Publishing Model: Print
Document type: English Abstract; Journal Article; Review
Languages: FRENCH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
This study reviews the various types of treatment used in infertility due to hyperandrogenism with the aim of answering the following three questions: How should these drugs be prescribed? What are their side-effects? What are the best diagnostic indications? Possibilities include ovulation inducers but also all types of treatment capable of improving the fertility of these women. The treatment of infertility due to adrenal hyperandrogenism is based upon glucocorticoids. This treatment must be continued for 3 months after conception, to attempt to avoid early spontaneous abortion. The first-line inducer in ovarian hyperandrogenismis is clomiphene citrate. The good results obtained using the combination of dexamethasone and clomiphene citrate are explained by an adrenal participation in this type of hyperandrogenism. In case of failure, and in addition to classical monotrophins:--pre-treatment using LHRH agonists avoids the onset of premature luteinisation but does not prevent the possibility of multiple pregnancies;--use of purified FSH reduces, though not sufficiently, the risks of multifollicular maturation but does not greatly increase the overall pregnancy rate;--the "slow" protocol with purified FSH reduces the incidence of multifollicular maturation. Should this fail, prior treatment with an LHRH agonist and if not the pulsed administration of LHRH in non-obese women can be suggested. Surgical treatment provides useful results in severe forms of sterility due to polycystic ovaries syndrome, with new per-celioscopic techniques.

7/3,AB/5
DIALOG(R)File 155:MEDLINE(R)
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09672000 PMID: 12284661 Record Identifier: 8021128; 00212526
Infertility: a health problem in the Muslim world.
Serour G I; El Ghar M; Mansour R T
Population sciences (Cairo, Egypt) (EGYPT) Jan 1991, 10 p41-58, Journal Code: 9425997
Publishing Model: Print TJ: POPULATION SCIENCES

Document type: In Vitro; Journal Article
Languages: ENGLISH
Main Citation Owner: PIP
Other Citation Owner: IND; PCP
Abstract Source: PIP
Record type: MEDLINE; Completed
Between November 1980-August 1989, physicians in Cairo, Egypt followed 1488 infertile couples. The study reported the extent of infertility, its etiology, and problems related to its management. Primary and secondary infertility affected 70.7% and 29.3% of the couples, respectively. Length of infertility ranged from 1 to 23 years (mean = 7.18 for primary infertility and 6.05 for secondary infertility). 306 husbands (20.6% of the couples) had either an insufficient sperm count (20 X 1 million), insufficient sperm motility (40%), or 40% abnormal sperm. Both the husband and wife of 181 couples (12.2%) suffered from infertility. The physicians could not identify the cause of infertility in 49 couples (3.3%). 952 wives (64% of the couples) were infertile. Tubal problems were mainly responsible for female infertility (42%) followed by ovulatory disorders (25.3%), multiple factors (23.4%), pelvic endometriosis (5.6%), and cervical effects (4.2). Various treatments included laparoscopic adhesiolysis in 30 patients, tubal microsurgery in 523 patients, induction of ovulation and monitoring (e.g., clomid and hCG) in 224 patients, in vitro fertilization (IVF) and embryo transfer (ET) in 256 patients, artificial insemination with husband's capacitated sperm along with ovulation induction in 114 couples, intrauterine synechia and septa via hysteroscopy in 17 patients, and abdominal myomectomy in 57 patients. The follow-up pregnancy rate for 523 microsurgery patients was 55.2% and 38% went full term. Only 51-63% of the couples could afford to pay for IVF and ET. Induction/monitoring of ovulation, or artificial insemination with husband's sperm all of which only the private sector provided. Patients had to wait for laparoscopy and microsurgery which were also available through government hospitals. These results demonstrate that prevention of infertility is preferable to treatment particularly in developing countries such as Egypt. Islam's view of infertility and family is also addressed.

7/3,AB/6
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

09307559 PMID: 2485374
[In vitro fertilization program. Preliminary results]
Programa de fecundacion in vitro. Resultados preliminares.
Crisosto C; Cheviakoff S; Vera J A; Ruttlant J; Arguello B; Romero C; Barros C
Clinica de Diagnostico Gineco-Obstetrica de Santiago.
Revista chilena de obstetricia y ginecologia (CHILE) 1989, 54 (6) p375-80; discussion 380-1, ISSN 0048-766X--Print Journal Code: 0404260
Publishing Model: Print
Document type: English Abstract; Journal Article
Languages: SPANISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Three infertile couples were submitted to in vitro fertilization and uterine embryo transfer (IVF+ET) and 7 to in vitro fertilization and pronuclear stage tubal transfer (IVF+PROST). In order to programmed menstruation Norethisterone, 10 mg daily, were administered during the cycle preceding the one of controlled ovarian hyperstimulation. In order to inhibit endogenous production of FSH and LH, leuprolide acetate, a Gn-RH agonist, was injected subcutaneously 1 mg daily during 6 days and 0.5 mg fovardly from the luteal phase of the cycle proceeding the one of hyperstimulation until the day of HCG administration. To achieve superovulation pure FSH (Metrodine), HMG (Pergonal) and HCG (Endocorion) were used. Cocyte retrieval was performed through transvaginal puncture under ultrasonographic control. For oocyte and embryo identification and classification, spermatozoa separation and capacitation and gamete insemination and incubation procedures habitual techniques were employed. Pronuclear embryo tubal transfer was performed through a laparoscope 17 hours after insemination and embryo transfer to the uterine cavity after 48 hours. Nine of 10 patients responded to gonadotrophin hyperstimulation and were submitted to ovarian puncture. 69 oocytes (7. per patient) were obtained. 59 (81.15% of which were mature. 74.55% of the insemnated oocytes fertilized. Two patients got pregnant: one, submitted to IVF+PROST, presently has a multiple pregnancy with triplets and the second, submitted to IVF+UT, had a missed abortion at 8 weeks of pregnancy.

7/3,AB/7
DIALOG(R)File 155:MEDLINE(R)
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08270832 PMID: 3556332
[Successful treatment of female infertility of hypothalamic origin using pulsed administration of gonadotropin-releasing hormone

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(LHRH)]
  Skuteczne leczenie niepłodności kobiecej pochodzenia podwzgorzowego za
pomoca pulsacyjnego podawania hormonu uwalniajacego gonadotropiny (LH
-RH).
  Grabinski M; Bolanowski M; Zalewski J; Zbrog U
  Ginekologia polska (POLAND)  Jan 1987,  58 (1)  p11-6,  ISSN 0017-0011
--Print  Journal Code: 0374641
  Publishing Model: Print
  Document type: Case Reports; English Abstract; Journal Article
  Languages: POLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
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? s (stimulation or stimulate)adj2 oogenesis and (fsh or lh or hcg)
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>>>Invalid syntax
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          485197  STIMULATION
           79171  STIMULATE
            5244  OOGENESIS
               6  (STIMULATION OR STIMULATE)(W)OOGENESIS
           24899  FSH
           39216  LH
           17552  HCG
      S8       0  (STIMULATION OR STIMULATE)()OOGENESIS AND (FSH OR LH OR
                  HCG)
? s (stimulation or stimulate)and oogenesis and (fsh or lh or hcg)
          485197  STIMULATION
           79171  STIMULATE
            5244  OOGENESIS
           24899  FSH
           39216  LH
           17552  HCG
      S9       57  (STIMULATION OR STIMULATE)AND OOGENESIS AND (FSH OR LH OR
                  HCG)
? s s9 and py>1998
              57  S9
         5491440  PY>1998
     S10      29  S9 AND PY>1998
? s t s10/3,ab/all
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     S11       0  T S10/3,AB/ALL
? t s10/3,ab/all

 10/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
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26502987    PMID: 17964574
  Role of gap junctions and protein kinase A during the development of
oocyte maturational competence in Ayu (Plecoglossus altivelis).
  Yamamoto Yoji; Yoshizaki Goro; Takeuchi Toshio; Soyano Kiyoshi; Patino
Reynaldo
  Department of Marine Biosciences, Tokyo University of Marine Science and
Technology, 4-5-7 Konan, Minato-ku, Tokyo 108-8477, Japan.
  General and comparative endocrinology (United States)  Feb 1 2008,
155 (3)  p789-95,  ISSN 0016-6480--Print  Journal Code: 0370735
  Publishing Model: Print-Electronic
  Document type: Journal Article; Research Support, U.S. Gov't, Non-P.H.S.
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  Meiotic resumption in teleost oocytes is induced by a maturation-inducing
hormone (MIH). The sensitivity of oocytes to MIH, also known as oocyte
maturational competence (CMC), is induced by LH via mechanisms that
are not fully understood. A previous study of Ayu (Plecoglossus altivelis)
showed the presence of functional heterologous gap junctions (GJs) between
oocytes and their surrounding granulosa cells. The objectives of this study
were to determine the role of ovarian GJs and of protein kinase A (PKA)
during the acquisition of CMC. We examined the effects of the specific GJ
inhibitor carbenoxolone (CBX) and 18alpha-glycyrrhetinic acid (alpha-GA) on
the LH(hCG)-dependent acquisition of CMC and on
MIH-(17,20beta-dihydroxy-4-pregnen-3-one)-dependent meiotic resumption;
measured the cAMP content of ovarian follicles during the hCG
-dependent acquisition of CMC; and determined the effects of PK activators
and inhibitors on hCG-dependent CMC. Production of follicular cAMP
increased during the hCG-dependent acquisition of CMC. Both GJ
inhibitors and the PKA inhibitor H8-dihydrochloride, but not the PKC
inhibitor GF109203X, suppressed the hCG-dependent acquisition of CMC
in a dose-dependent manner. The PKA activator forskolin induced CMC with a
similar potency to hCG. Unlike previous observations with teleosts
where disruption of heterologous GJ either blocks or stimulates meiotic
resumption, treatment with GJ inhibitors did not affect MIH-dependent
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meiotic resumption in maturationally competent follicles of Ayu. These observations suggest that ovarian GJs are essential for LH-dependent acquisition of CMC but not for MIH-dependent meiotic resumption, and that the stimulation of CMC by LH is mediated by cAMP-dependent PKA. They are also consistent with the view that a precise balance between GJ-mediated signals (positive or negative) and oocyte maturational readiness is required for hormonally regulated meiotic resumption.

10/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
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26481323 PMID: 18377904
The gonadotropin receptors FSH-R and LH-R of Atlantic halibut (Hippoglossus hippoglossus)-2. Differential follicle expression and asynchronous oogenesis.
Kobayashi Tamae; Pakarinen Pirjo; Torgersen Jacob; Huhtaniemi Ilpo; Andersen Oivind
Institute of Aquaculture Research, P.O. Box 5010, 1430 Aas, Norway; Department of Animal and Aquaculture Sciences, University of Life Sciences, P.O. Box 5003, Aas, Norway.
General and comparative endocrinology (United States) May 1 2008, 156 (3) p595-602, ISSN 0016-6480--Print Journal Code: 0370735
Publishing Model: Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Data Review
The biological activity and spatio-temporal expression patterns of the gonadotropin receptors FSH-R and LH-R were examined in the repetitive spawner Atlantic halibut to elucidate the gonadotropic regulation of the asynchronous follicle development. The cloned receptors were expressed in mammalian COS-7 cells, and stimulation with sea bass FSH and LH increased the cAMP production. The halibut FSH-R and LH-R genes were shown to be highly expressed in the gonads of sexually mature fish, but the transcripts were also found in extra-gonadal tissues such as pituitary and brain. Different expression patterns of FSH-R and LH-R in the developing follicles were documented by semi-quantitative RT-PCR. Abundant FSH-R mRNA was found in the small follicles during primary growth and vitellogenesis, and the signals were localized to the granulosa cells by in situ hybridization. In contrast, follicular LH-R mRNA was hardly detectable during the early stages. Conversely, in follicles during final maturation FSH-R mRNA levels tended to decrease, while the expression of LH-R was highly upregulated. Whereas the pituitary FSH and LH are asynchronously expressed in annual spawners, both gonadotropins were expressed in the female halibut pituitary throughout the reproductive cycle, except in the prespawning females. Hence, the sequential gonadotropic activation of ovarian follicle growth and maturation in repetitive spawners is probably regulated by modulating the temporal expression of FSH-R and LH-R in the follicle membrane.

10/3,AB/3
DIALOG(R)File 155:MEDLINE(R)
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26026974 PMID: 17884935
Meiotic maturation of incompetent prepubertal sheep oocytes is induced by paracrine factor(s) released by gonadotropin-stimulated oocyte-cumulus cell complexes and involves mitogen-activated protein kinase activation.
Cecconi Sandra; Mauro Annunziata; Capacchietti Giulia; Berardinelli Paolo ; Bernabo Nicola; Di Vincenzo Anna Rita; Mattioli Mauro; Barboni Barbara
Department of Biomedical Sciences and Technologies, University of L'Aquila, 67100 L'Aquila, Italy. sandra.cecconi@cc.univaq.it
Endocrinology (United States) Jan 2008, 149 (1) p100-7, ISSN 0013-7227--Print Journal Code: 0375040
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
In this study, sheep oocyte-cumulus cell complexes (COC) derived from medium (M) antral follicles (M-COC) were in vitro matured alone or in coculture with COC derived from small (S) antral follicles (S-COC) to investigate the contribution of cumulus cells (CC) and oocytes to the process of oocyte meiotic maturation and cumulus expansion (CE). Experiments were conducted with or without gonadotropins (FSH/LH). Regardless of culture conditions, about 12% of S-oocytes reached the metaphase II stage, and S-CC showed a low degree of CE. In contrast, both maturational processes were significantly stimulated by gonadotropins in M-COC. However, about 48% of S-oocytes progressed to metaphase II, and S-CC expanded after coculture with gonadotropin-stimulated M-COC and M-CC but not with mural granulosa cells. Both maturational processes were

inhibited when S-COC were cocultured with M-denuded oocytes, or when S-denuded oocytes were cocultured with M-CC. The capacity of these paracrine factor(s) to activate the MAPK pathway in somatic and germ cells of S-complexes was investigated. It was found that MAPK kinase/MAPK phosphorylation levels in M-COC but not in S-COC were significantly increased by gonadotropins, first in CC and later in the oocytes. Kinase phosphorylations were activated only in S-oocytes cocultured with M-COC or M-CC. These results demonstrate that soluble factors specifically produced by M-CC are capable to induce meiotic maturation and CE in S-complexes by acting via CC. These factors can induce MAPK activation only in S-oocytes, whose meiotic arrest could be due to the inability of surrounding CC to respond to gonadotropin stimulation.

10/3,AB/4
DIALOG(R)File 155:MEDLINE(R)
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25614633 PMID: 18028753
Ovarian theca cells in follicular function.
Tajima Kimihisa; Orisaka Makoto; Mori Takahide; Kotsuji Fumikazu
Department of Obstetrics and Gynecology, Faculty of Medical Sciences, University of Fukui, 23 Shimoaizuki, Matsuoka, Fukui 910-1193, Japan.
Reproductive biomedicine online (England) Nov 2007, 15 (5) p591-609, ISSN 1472-6483--Print Journal Code: 101122473
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The role of theca cells in every aspect of ovarian follicular function is reviewed. A distinguishing feature of theca cells may be their ability to initiate follicle growth on differentiation from cortical stromal cells, stimulate follicle growth by granulosa cell mitosis through FSH-induced androgen receptor, and cause androgen-stimulated receptor formation of FSH. As LH not only stimulates androgen production by theca cells at tonic levels, but also induces morphological luteinization in addition to androgenesis at surge levels, the dual action concept of LH is proposed. Maturation of the selected dominant follicle and atresia of subordinate antral follicles is interpreted by this concept. Two-way signalling between oocytes and somatic theca cells with growth factors is shown to play a pivotal role in preantral folliculogenesis and atresia. Thus, theca cells have a more significant role in follicular function than previously thought.

10/3,AB/5
DIALOG(R)File 155:MEDLINE(R)
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25201647 PMID: 17714774
Effects of ovarian stimulation, with and without human chorionic gonadotrophin, on oocyte meiotic and developmental competence in the marmoset monkey (Callithrix jacchus).
Grupen C G; Gilchrist R B; Nayudu P L; Barry M F; Schulz S J; Ritter L J; Armstrong D T
Research Centre for Reproductive Health, School of Paediatrics and Reproductive Health, The University of Adelaide, Adelaide, SA 5005, Australia. cgrupen@etsci.usyd.edu.au
Theriogenology (United States) Oct 1 2007, 68 (6) p861-72, ISSN 0093-691X--Print Journal Code: 0421510
Publishing Model: Print-Electronic
Document type: Clinical Trial; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
A reliable ovarian stimulation protocol for marmosets is needed to enhance their use as a model for studying human and non-human primate oocyte biology. In this species, a standard dose of hCG did not effectively induce oocyte maturation in vivo. The objectives of this study were to characterize ovarian response to an FSH priming regimen in marmosets, given without or with a high dose of hCG, and to determine the meiotic and developmental competence of the oocytes isolated. Ovaries were removed from synchronized marmosets treated with FSH alone (50 IU/d for 6 d) or the same FSH treatment combined with a single injection of hCG (500 IU). Cumulus-oocyte complexes (COCs) were isolated from large (>1.5mm) and small (0.7-1.5mm) antral follicles. In vivo-matured oocytes were subsequently activated parthenogenetically or fertilized in vitro. Immature oocytes were subjected to in vitro maturation and then activated parthenogenetically. Treatment with FSH and hCG combined increased the number of expanded COCs from large antral follicles compared with FSH alone (23.5 +/- 9.3 versus 6.4 +/- 2.7, mean +/- S.E.M.). Approximately 90% of oocytes surrounded by expanded cumulus cells at the time of isolation were meiotically mature. A

blastocyst formation rate of 47% was achieved following fertilization of in vivo-matured oocytes, whereas parthenogenetic activation failed to induce development to the blastocyst stage. The capacity of oocytes to complete meiosis in vitro and cleave was positively correlated with follicle diameter. A dramatic effect of follicle size on spindle formation was observed in oocytes that failed to complete meiosis in vitro. Using the combined FSH and hCG regimen described in this study, large numbers of in vivo matured marmoset oocytes could be reliably collected in a single cycle, making the marmoset a valuable model for studying oocyte maturation in human and non-human primates.

10/3, AB/6
DIALOG(R)File 155:MEDLINE(R)
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17597284 PMID: 17391547
Spontaneous and LH-induced maturation in Bufo arenarum oocytes: importance of gap junctions.
Toranzo G Sanchez; Cherino J; Zelarayan L; Bonilla F; Buhler M I
Departamento de Biologia del Desarrollo, San Miguel de Tucuman, Argentina.
Zygote (Cambridge, England) (England) Feb 2007, 15 (1) p65-80, ISSN 0967-1994-Print Journal Code: 9309124
Publishing Model Print
Document type: In Vitro; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
It has been demonstrated in Bufo arenarum that fully grown oocytes are capable of meiotic resumption in the absence of a hormonal stimulus if they are deprived of their follicular envelopes. This event, called spontaneous maturation, only takes place in oocytes collected during the reproductive period, which have a metabolically mature cytoplasm. In Bufo arenarum, progesterone acts on the oocyte surface and causes modifications in the activities of important enzymes, such as a decrease in the activity of adenylate cyclase (AC) and the activation of phospholipase C (PLC). PLC activation leads to the formation of diacylglycerol (DAG) and inositol triphosphate (IP(3)), second messengers that activate protein kinase C (PKC) and cause an increase in intracellular Ca(2+). Recent data obtained from Bufo arenarum show that progesterone-induced maturation causes significant modifications in the level and composition of neutral lipids and phospholipids of whole fully grown ovarian oocytes and of enriched fractions in the plasma membrane. In amphibians, the luteinizing hormone (LH) is responsible for meiosis resumption through the induction of progesterone production by follicular cells. The aim of this work was to study the importance of gap junctions in the spontaneous and LH-induced maturation in Bufo arenarum oocytes. During the reproductive period, Bufo arenarum oocytes are capable of undergoing spontaneous maturation in a similar way to mammalian oocytes while, during the non-reproductive period, they exhibit the behaviour that is characteristic of amphibian oocytes, requiring progesterone stimulation for meiotic resumption (incapable oocytes). This different ability to mature spontaneously is coincident with differences in the amount and composition of the phospholipids in the oocyte membranes. Capable oocytes exhibit in their membranes higher quantities of phospholipids than incapable oocytes, especially of PC and PI, which are precursors of second messengers such as DAG and IP(3). The uncoupling of the gap junctions with 1-octanol or halothane fails to induce maturation in follicles from the non-reproductive period, whose oocytes are incapable of maturing spontaneously. However, if the treatment is performed during the reproductive period, with oocytes capable of undergoing spontaneous maturation, meiosis resumption occurs in high percentages, similar to those obtained by manual defolliculation. Interestingly, results show that LH is capable of inducing GVBD in both incapable oocytes and in oocytes capable of maturing spontaneously as long as follicle cells are present, which would imply the need for a communication pathway between the oocyte and the follicle cells. This possibility was analysed by combining LH treatment with uncoupling agents such as 1-octanol or halothane. Results show that maturation induction with LH requires a cell-cell coupling, as the uncoupling of the gap junctions decreases GVBD percentages. Experiments with LH in the presence of heparin, BAPTA/AM and theophylline suggest that the hormone could induce GVBD by means of the passage of IP(3) or Ca(2+) through the gap junctions, which would increase the Ca(2+) level in the oocyte cytoplasm and activate phosphodiesterase (PDE), thus contributing to the decrease in cAMP levels and allowing meiosis resumption.

10/3, AB/7
DIALOG(R)File 155:MEDLINE(R)
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17104751 PMID: 16595009
Comparative maturation of cynomolgus monkey oocytes in vivo and in vitro.

Yin Hang; Duffy Diane M; Gosden Roger G
The Jones Institute for Reproductive Medicine, Department of Obstetrics and Gynaecology, Eastern Virginia Medical School, Norfolk, VA 23507, USA. Hay2003@med.cornell.edu
Reproductive biology and endocrinology : RB&E (England) 2006, 4 p14, ISSN 1477-7827--Electronic Journal Code: 101153627
Contract/Grant No.: HD39872; HD; United States NICHD
Publishing Model: Electronic
Document type: Comparative Study; Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: In vitro maturation (IVM) of oocytes followed by fertilization in vitro (IVF) and embryo transfer offers an alternative to conventional IVF treatment that minimises drug administration and avoids ovarian hyperstimulation. However, the technique is less efficient than maturation in vivo. In the present study, a non-human primate model was used to address the hypothesis that the number of oocytes is increased and their nuclear and cytoplasmic maturity after IVM are improved when maturation is initiated in vivo by priming with hCG. METHODS: Young, adult cynomolgus monkeys were given recombinant human (rh) gonadotropins to stimulate the development of multiple follicles, and oocytes were aspirated 0, 12, 24, or 36 h after injection of an ovulatory dose of rhCG. The nuclear status of oocytes was determined at the time of recovery and after culture for a total elapsed time of 40-44 hours after hCG. RESULTS: Priming with hCG significantly increased the number of oocytes harvested, especially after delaying aspiration for 24 h or longer. Nuclear maturation after the full period in culture was also enhanced by priming: 71.5, 83.6, and 94.6% of oocytes collected at 0, 12, and 24 h hCG had progressed to MI by the end of the culture period, compared to 87.8% of oocytes that were retrieved at 36 h. A large proportion of oocytes reaching the MI stage had either or both abnormal spindles (>40% and misaligned chromosomes (>60%, judging by immunofluorescence microscopy, but these abnormalities were independent of culture time. The mitochondria were evenly distributed throughout the cytoplasm at all stages of maturation. Importantly, there was no microscopic evidence that the duration of culture had any injurious effects on the cells. CONCLUSION: In conclusion, the evidence supports this non-human primate as a model for human IVM and the practice of priming with hCG to promote developmental potential.

10/3,AB/8
DIALOG(R)File 155:MEDLINE(R)
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16920540 PMID: 16297918
Steroidogenic activities of follicle-stimulating hormone in the ovary of Japanese eel, Anguilla japonica.
Kamei Hiroyasu; Kaneko Toyoji; Aida Katsumi
Department of Aquatic Bioscience, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Bunkyo, Tokyo 113-8657, Japan. kamei@marine.fs.a.u-tokyo.ac.jp
General and comparative endocrinology (United States) Apr 2006, 146 (2) p83-90, ISSN 0016-6480--Print Journal Code: 0370735
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
To clarify the physiological functions of follicle-stimulating hormone (FSH) during oogenesis in Japanese eel, Anguilla japonica, the steroidogenic activities of recombinant Japanese eel FSH (rjeFSH) were assessed in the eel ovary. Female eel were injected with salmon pituitary homogenate to enhance the ovarian development, and the ovaries at different developmental stages were subjected to steroidogenic bioassay. These ovaries could be classified into three types according to oocyte growth and development of ovarian follicular cells. The type-A ovary possessed poorly developed follicular cells around pre- or early vitellogenic oocytes, and rjeFSH did not induce sex steroid secretion. Testosterone (T) secretion was stimulated by rjeFSH in the type-B ovary with developed theca cells and undeveloped granulosa cells around early to mid-vitellogenic oocytes, whereas estradiol-17beta (E2) secretion was not enhanced. The rjeFSH stimulated both T and E2 secretion in a dose-dependent manner from the type-C ovary with fully developed theca and granulosa cells around mid-vitellogenic oocytes. Salmon GTH fraction (sGTH) and a membrane permeable cAMP analogue, 8-bromo-cAMP (8-Br-cAMP) also enhanced T and E2 secretion from the type-C ovary. Human chorionic gonadotropin (hCG) similarly enhanced T secretion, but failed to stimulate E2 secretion from the type-C ovary, suggesting different effects on steroidogenic activities between eel FSH and hCG in eel ovary. There was a positive correlation between the oocyte diameter and E2 secretion from eel ovaries stimulated by rjeFSH. These results suggest that aromatase activity is accelerated by eel FSH in the granulosa cells, which develop

following theca cell development in this species.

10/3,AB/9
DIALOG(R)File 155:MEDLINE(R)
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16902649 PMID: 16508140
cDNA cloning, genomic structure and expression analysis of the bovine lanosterol 14alpha-demethylase (CYP51) in gonads.
Wang Fengchao; Shen Yue; Song Xiaoming; Xia Guoliang; Chen Xiu; Zhou Bo; Lei Lei
College of Biological Science, China Agricultural University, Beijing, PR China.
Biological & pharmaceutical bulletin (Japan) Mar 2006, 29 (3) p430-6, ISSN 0918-6158--Print Journal Code: 9311984
Publishing Model: Print
Document type: In Vitro; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Meiosis activating sterol (MAS), the intermediate of cholesterol biosynthesis, is an important substance to stimulate oocytes maturation in FSH-induced signal transduction pathway. Lanosterol 14alpha-demethylase (CYP51) converts lanosterol to MAS. Although MAS is firstly isolated from bovine testis, the information about bovine CYP51 gene and its expression is little. In present studies, the cDNA cloning, genomic structure, chromosomal mapping, and expression patterns of bovine CYP51 were demonstrated. The cDNA coding bovine CYP51 contains a 1509 bp open reading frame and a 1119 bp 3' untranslated region. And the bovine CYP51 gene includes 10 exons and spans about 17 kb. Screening the cattle RH5000 panel bovine CYP51 is mapped to chromosome 4 (0cR). The sequenced promoter region is TATA-less and contains several highly conserved regulatory elements, such as GC-box, cAMP-responsive elements (CRE), sterol regulatory element (SRE) which is important fragment for its transcription. No evidence of processed pseudogenes is found using long PCR and Southern blot. Northern blot analysis reveals that an approximately 2.7 kb mRNA is expressed in all the examined bovine tissues, while a 1.8 kb mRNA is found only in the mature bovine testis where the MAS is accumulated. Immunochemistry analysis shows that leydig cells express the highest level of the CYP51 protein in testis. Among different stages follicles it is localized primarily to the oocytes with the level varying slightly. Granulosa cells of primordial, primary and secondary follicles show background staining. While granulosa cells facing the antrum and cumulus granulosa cells of antral follicles show considerably heavier staining. The highest level is expressed in corpus lutea. These data indicate a stage- and cell type-specific expression of CYP51 protein in bovine oogenesis.

10/3,AB/10
DIALOG(R)File 155:MEDLINE(R)
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16720859 PMID: 16322539
Stops and starts in mammalian oocytes: recent advances in understanding the regulation of meiotic arrest and oocyte maturation.
Mehlmann Lisa M
Department of Cell Biology, University of Connecticut Health Center, 263 Farmington Ave., Farmington, Connecticut 06032, USA. lmehlman@neuron.uchc.edu
Reproduction (Cambridge, England) (England) Dec 2005, 130 (6) p791-9, ISSN 1470-1626--Print Journal Code: 100966036
Publishing Model: Print
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Mammalian oocytes grow and undergo meiosis within ovarian follicles. Oocytes are arrested at the first meiotic prophase, held in meiotic arrest by the surrounding follicle cells until a surge of LH from the pituitary stimulates the immature oocyte to resume meiosis. Meiotic arrest depends on a high level of cAMP within the oocyte. This cAMP is generated by the oocyte, through the stimulation of the G(s) G-protein by the G-protein-coupled receptor, GPR3. Stimulation of meiotic maturation by LH occurs via its action on the surrounding somatic cells rather than on the oocyte itself. LH induces the expression of epidermal growth factor-like proteins in the mural granulosa cells that act on the cumulus cells to trigger oocyte maturation. The signaling pathway between the cumulus cells and the oocyte, however, remains unknown. This review focuses on recent studies highlighting the importance of the oocyte in producing cAMP to maintain arrest, and discusses possible targets at the level of the oocyte on which LH could act to stimulate meiotic

resumption.

10/3,AB/11
DIALOG(R)File 155:MEDLINE(R)
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16559460 PMID: 16123237
Protein kinases influence bovine oocyte competence during short-term treatment with recombinant human follicle stimulating hormone.
Ali Atef; Sirard Marc-Andre
Centre de Recherche en Biologie de la Reproduction (CRBR), Department of Animal Science, Laval University, Ste-Foy, Quebec, Canada, G1K 7P4.
Reproduction (Cambridge, England) (England) Sep 2005, 130 (3) p303-10, ISSN 1470-1626--Print Journal Code: 100966036
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The aim of this study was to investigate the effect of short-term treatment (first 2 or 6 h) with recombinant human follicle-stimulating hormone (r-hFSH) during in vitro maturation (IVM) on the developmental competence of bovine oocytes. The roles of protein kinase A (PKA) and protein kinase C (PKC) (possibly involved in FSH response), were investigated using activators (Sp-cAMPS, PMA) or inhibitors (Rp-cAMPS, sphingosine) of these two protein kinases, respectively. The developmental competence of bovine oocytes was measured by the rate of blastocyst formation after in vitro fertilization (IVF). Our results showed that when cumulus-oocyte complexes (COCs) were cultured with r-hFSH for the first 6 h, a highly significant ($P < 0.0001$) improvement is seen in blastocyst development rate as a proportion of oocytes in culture compared with those matured with r-hFSH for the first 2 or 24 h. A transient exposure (6 h) to the highest dose (100 microM) of forskolin (an activator of adenylate cyclase) increased ($P < 0.05$) the rate of blastocyst formation. But the PKA inhibitors (Rp-cAMPS) did not affect the stimulatory effects of r-hFSH on the blastocyst yield. However, stimulation of PKC by low doses of PMA (0.1-0.5 microM) during short-term treatment, enhanced ($P < 0.0001$) the developmental capacity of oocytes, while sphingosine (a specific inhibitor of PKC) inhibited ($P < 0.05$) the stimulatory effects of r-hFSH on the rate of blastocyst formation. Our results indicate that although the developmental capacity of bovine oocytes in vitro can be modulated by both the PKA and the PKC pathways, the activation of PKC during short-term treatment can mimic the effect of r-hFSH on the cytoplasmic maturation in bovine oocytes in vitro.

10/3,AB/12
DIALOG(R)File 155:MEDLINE(R)
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16459751 PMID: 15982453
Particularities of reproduction and oogenesis in teleost fish compared to mammals.
Jalabert Bernard
Groupe Sexualite et Reproduction des Poissons, Institut National de la Recherche Agronomique, SCRIBE, Campus de Beaulieu, 35042 Rennes Cedex, France. Bernard.Jalabert@rennes.inra.fr
Reproduction, nutrition, development (France) May-Jun 2005, 45 (3) p261-79, ISSN 0926-5287--Print Journal Code: 8913069
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Compared to mammals, teleost reproduction presents many original features. Reproductive strategies of species are diversified into numerous adaptations to a large variety of aquatic environments. This diversity may concern sexuality, spawning and parental behaviour, sensitivity to environmental factors, and specific features of gametogenesis such as the duration of vitellogenesis, and egg morphology. Sexuality presents a variety of natural modalities, from gonochorism to hermaphrodism. The absence of definitive arrest of body growth in the adult of most species gives a particular interest to the practical control of growth-reproduction interactions. Vitellogenesis, which represents an important metabolic effort for the maternal organism, involves the synthesis of vitellogenin, a specific glycolipo-phosphoprotein produced in the liver under estradiol stimulation, and its incorporation into oocytes by a receptor-mediated process. Both estradiol synthesis in follicle cells and vtg uptake by vitellogenic follicles appear to be mainly controlled by FSH. Oocyte maturation is directly triggered by a progestin, or MIS (maturation inducing steroid) synthesised in follicle cells mainly under LH control, and acting through the non-genomic activation of a membrane receptor. Practical applications of some of these particularities result mainly from the external character of the fertilisation process and of

embryonic development, which allows manipulating respectively egg chromosome stocks and sex differentiation. Moreover, the sensitivity of sex differentiation to exogenous factors favours the development of practical methods to control the sex of farmed populations. Finally, the sensitivity of reproductive mechanisms to xenobiotics has led to various kinds of bioassays for putative pollutants.

10/3,AB/13
DIALOG(R)File 155:MEDLINE(R)
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16184083 PMID: 15459120
Epidermal growth factor family members: endogenous mediators of the ovulatory response.
Ashkenazi H; Cao X; Motola S; Popliker M; Conti M; Tsafriri A
The Bernhard Zondek Hormone Research Laboratory, Department of Biological Regulation, The Weizmann Institute of Science, Rehovot 76100, Israel.
Endocrinology (United States) Jan 2005, 146 (1) p77-84, ISSN 0013-7227--Print Journal Code: 0375040
Contract/Grant No.: HD20788; HD; United States NICHD; U54-HD 31398; HD; United States NICHD
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Previous studies showed that epidermal growth factor (EGF) and TGFalpha mimic the action of LH on the resumption of oocyte maturation. We tested whether EGF-like agents, such as amphiregulin (AR), epiregulin (ER), and betacellulin (BTC), also mediate the LH stimulation of the ovulatory response in the rat. LH induced transient follicular expression of AR, ER, and BTC mRNA, reaching a maximum after 3-h incubation. Furthermore, the addition of ER, AR, and BTC to the culture medium could mimic some of LH actions. AR and ER fully simulated LH-induced resumption of meiosis in vitro, whereas BTC was less effective. To study the putative involvement of EGF-like factors in mediation of LH signal, the effect of the EGF receptor kinase inhibitor AG1478 was tested. When added with LH, AG1478, but not its inactive analog AG43, reduced EGF receptor phosphorylation and oocyte maturation compared with follicles treated with LH only. In addition to the inhibition of resumption of meiosis, AG1478 administration into the bursa (3 microg/bursa) resulted in 51% (P < 0.0005) inhibition of ovulation in the treated ovaries, compared with the untreated contralateral ones, as well as to the vehicle-treated ovaries (P < 0.02). LH, as well as ER, induced the expression of genes associated with the ovulatory response like rat hyaluronan synthase-2, cyclooxygenase-2, and TNFalpha-stimulated gene 6 mRNA, whereas AG1478 inhibited this effect of LH. Release of EGF-like factors from the membrane is dependent on activated metalloproteases. Indeed, Galardin, a broad-spectrum metalloprotease inhibitor, but not a specific matrix metalloprotease 2 and 9 inhibitor, suppressed meiotic maturation induced by LH. Conversely, meiotic maturation induced by ER was not affected by Galardin, thus, supporting the notion that LH releases follicular membrane-bound EGF-like agents. In summary, EGF-like factors such as ER, AR, and BTC seem to mediate, at least partially, the LH stimulation of oocyte maturation, ovulatory enzyme expression, and ovulation.

10/3,AB/14
DIALOG(R)File 155:MEDLINE(R)
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16129757 PMID: 15643685
[Biological assessment criteria during antagonist protocols]
Criteres d'evaluation biologique au cours des protocoles antagonistes.
Plachot M
Centre Hospitalier Intercommunal Jean-Rostand, Sevres, France.
Journal de gynecologie, obstetrique et biologie de la reproduction (France) Oct 2004, 33 (6 Pt 2) p3S32-5, ISSN 0368-2315--Print Journal Code: 0322206
Publishing Model: Print
Document type: English Abstract; Journal Article
Languages: FRENCH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Until recently, gonadotropin-releasing hormone (GnRH) agonists were the only choice available to physicians for prevention of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian stimulation. The recent approval of GnRH antagonists for this indication gives clinicians some new options. In several trials performed, the GnRH antagonist regimens have been associated with a slightly lower pregnancy and implantation rates than the established GnRH agonist protocols. This review summarizes the main studies concerning oocyte

quality and fertilization in IVF cycles with GnRH antagonists. As a result, there is no difference between GnRH agonist and GnRH antagonists concerning oocyte maturation and fertilization rates. There are very few data about the incidence of oocyte morphology anomalies in IVF cycles with antagonists.

10/3,AB/15
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16129750 PMID: 15643678
[The respective roles of gonadotrophins on follicular growth and oocyte maturation]
Roles respectifs des gonadotrophines sur la croissance folliculaire et la maturation ovocytaire.
Hillier S
Centre for Reproductive Biology, University of Edinburgh, UK.
Journal de gynecologie, obstetrique et biologie de la reproduction (France) Oct 2004, 33 (6 Pt 2) p3S11-4, ISSN 0368-2315--Print
Journal Code: 0322206
Publishing Model: Print
Document type: English Abstract; Journal Article
Languages: FRENCH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Around 400 follicles sequentially mature and ovulate during an average woman's reproductive lifetime. Follicular growth to the stage of antrum formation is independent of gonadotrophic stimulation and might be dependent of androgen exposure. During the follicular phase, effects of LH must be considered according to the stages of follicular development: in the early follicular phase, LH acts through specific receptors, constitutively present on thecal cells, for stimulating androgen production. Androgens seem to be positively involved in the folliculogenesis in primates. Indeed, a positive correlation has been recently established between androgen receptor expression and follicular cell proliferation. Nevertheless, LH, beyond a certain ceiling level, suppresses granulosa proliferation, and initiates atresia or premature luteinisation. The development-related response to LH shown by the pre-ovulatory follicle raises the possibility that exogenous LH might be used as an adjunct to therapy with exogenous FSH in clinical ovulation induction regimens where the aim is to induce monovulation. Rec LH will allow the opportunity to provide LH support in a flexible and responsive way, with the possibility of fine tuning FSH action on follicular development. Availability of pure, standalone LH will allow a re-evaluation of follicular stimulation based on physiological principles, leading to new treatment protocols.

10/3,AB/16
DIALOG(R)File 155:MEDLINE(R)
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16076171 PMID: 15269103
Meiosis-activating sterol synthesis in rat preovulatory follicle: is it involved in resumption of meiosis?
Cao Xiumei, Pomerantz Seymour H, Popliker Malka, Tsafriri Alex
Bernhard Zondek Hormone Research Laboratory, Department of Biological Regulation, The Weizmann Institute of Science, Rehovot 76100, Israel.
Biology of reproduction (United States) Dec 2004, 71 (6) p1807-12, ISSN 0006-3363--Print Journal Code: 0207224
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Meiosis-activating sterol (MAS) was shown to overcome the inhibitory effect of hypoxanthine on spontaneous maturation of mouse oocytes and was suggested to mediate the stimulation of meiosis by gonadotropins. Follicular fluid (FF)-MAS is synthesized by cytochrome P450 lanosterol 14alpha-demethylase (LDM). Follicular LDM was preferentially localized in oocytes by immunohistochemistry. Using [3H]acetate or R-[5-3H]mevalonate as precursors as well as high-performance liquid chromatographic and thin-layer chromatographic separation, we have measured the concentrations of de novo-synthesized lanosterol, FF-MAS, and cholesterol in rat graafian follicles, cumulus-oocyte complexes (COCs), and denuded oocytes (DOs) treated with LH, AY-9944 (an inhibitor of Delta14-reductase, which was anticipated to increase FF-MAS levels by inhibiting its metabolism), or both after 8 h of culture. In follicles, both LH and AY-9944 increased the accumulation of FF-MAS as compared to controls. In COCs, AY-9944 caused a marked increase in FF-MAS, but we were unable to detect accumulation of FF-MAS in DOs. Neither the endogenous increases in FF-MAS accumulation nor the addition of FF-MAS to the culture medium could overcome the inhibition on resumption of meiosis by phosphodiesterase inhibitors. Compared to LH-induced resumption of meiosis in

follicles, that induced by AY-9944 was much delayed. These results call into question any role of FF-MAS as an obligatory mediator of LH activity on germinal vesicle breakdown. The discrepancy between the positive staining for LDM in oocytes and our inability to detect de novo synthesized FF-MAS in DCs may relate to the sensitivity of the methodology employed and either the number of oocytes used or a deficiency in LDM synthetic activity in such oocytes. Further studies are required to confirm any of these alternatives.

10/3, AB/17
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16036657 PMID: 15509704
A close correlation in the expression patterns of Af-6 and Usp9x in Sertoli and granulosa cells of mouse testis and ovary.
Sato Takeshi; Kanai Yoshiakira; Nomra Takashi; Kanai-Azuma Masami; Taya Shinichiro; Matsui Toshiyasu; Ishii Maki; Kawakami Hayato; Kurohmaru Masamichi; Kaibuchi Kozo; Wood Stephen A; Hayashi Yoshihiro
Department of Veterinary Anatomy, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113-8657, Japan.
Reproduction (Cambridge, England) (England) Nov 2004, 128 (5) p583-94, ISSN 1470-1626--Print Journal Code: 100966036
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Usp9x, an X-linked deubiquitylating enzyme, is stage dependently expressed in the supporting cells (i.e. Sertoli cells and granulosa cells) and germ cells during mouse gametogenesis. Af-6, a cell junction protein, has been identified as a substrate of Usp9x, suggesting a possible association between Usp9x and Af-6 in spermatogenesis and oogenesis. In this study, we examined the expression pattern of Af-6 and Usp9x and their intracellular localization in testes and ovaries of mice treated with or without pregnant mare serum gonadotropin (PMSG), an FSH-like hormone. In both testes and ovaries, Af-6 expression was predominantly observed in supporting cells, as well as in steroidogenic cells, but not in any germ cells. In Sertoli cells, Af-6 was continuously expressed throughout postnatal and adult stages, where both Af-6 and Usp9x were enriched at the sites of Sertoli-Sertoli and Sertoli-spermatid junctions especially at stages XI-VI. In the granulosa cells, Af-6, as well as Usp9x, was highly expressed in primordial and primary follicles, but its expression rapidly decreased after the late-secondary follicle stage. Interestingly, in PMSG-treated mice, the expression levels of Af-6 and Usp9x were synchronously enhanced, slightly in Sertoli cells and strongly in granulosa cells of the late-secondary and Graafian follicles. Such closely correlated expression patterns between Af-6 and Usp9x clearly suggest that Af-6 may be deubiquitylated by Usp9x in both Sertoli and granulosa cells. It further suggests that the post-translational regulation of Af-6 by Usp9x may be one potential pathway to control the cell adhesion dynamics in mammalian gametogenesis.

10/3, AB/18
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15937335 PMID: 15333782
Cumulus expansion and glucose utilisation by bovine cumulus-oocyte complexes during in vitro maturation: the influence of glucosamine and follicle-stimulating hormone.
Sutton-McDowall Melanie L; Gilchrist Robert B; Thompson Jeremy G
Research Centre for Reproductive Health, Department of Obstetrics and Gynaecology, The University of Adelaide, The Queen Elizabeth Hospital, Woodville Road, Woodville, South Australia 5011, Australia.
Reproduction (Cambridge, England) (England) Sep 2004, 128 (3) p313-9, ISSN 1470-1626--Print Journal Code: 100966036
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Glucose is an important metabolite and its presence during in vitro oocyte maturation (IVM) can have profound effects on the oocyte's developmental capacity. We have demonstrated that glucose uptake increases over a 24 h IVM period, with most accounted for as l-lactate production. However, as maturation proceeds, l-lactate production remains constant, suggesting an alternative role for glucose metabolism. We hypothesised that in the latter stages of oocyte maturation, glucose not accounted for by l-lactate production is utilised for FSH-stimulated extracellular matrix (ECM) synthesis. To examine precursor utilisation for synthesis of ECM, bovine cumulus-oocyte complexes (COCs) were matured in +/- FSH and/or glucosamine (an alternative substrate of matrix components).

Measurements included COC diameters, glucose consumption and l-lactate production in spent media and [U-(14)C]glucose incorporation into ECM. FSH significantly stimulated both diameter and glucose consumption during 20-24 h maturation compared with unstimulated complexes; although co-incubation with glucosamine and FSH decreased total glucose consumption 1.7-fold compared with FSH alone ($P < 0.05$). Furthermore, there was a linear relationship between glucose and l-lactate metabolism in the presence of glucosamine, suggesting that the majority of glucose was being utilised for l-lactate production via glycolysis. In the presence of glucosamine, twofold less [U-(14)C]glucose was incorporated into matrix compared with COCs cultured without glucosamine. These results support the hypothesis that there is a link between glucose and glucosamine uptake in FSH-stimulated ECM synthesis. Furthermore, glucose has multiple fates within the COC during maturation and levels of utilisation are dependent on the composition of the maturation environment.

10/3, AB/19
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15830853 PMID: 14985242
Progesterone promotes oocyte maturation, but not ovulation, in nonhuman primate follicles without a gonadotropin surge.
Borman Sherri M; Chaffin Charles L; Schwinof Kristine M; Stouffer Richard L; Zelinski-Wooten Mary B
Oregon National Primate Research Center, Beaverton, Oregon 97006, USA.
Biology of reproduction (United States) Jul 2004, 71 (1) p366-73. ISSN: 0006-3363--Print Journal Code: 0207224
Contract/Grant No.: 2T32 HD07133; HD; United States NICHD; HD20869; HD; United States NICHD; RR00163; RR; United States NCRR; U54 HD18185; HD; United States NICHD
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
During the periovulatory interval, intrafollicular progesterone (P) prevents follicular atresia and promotes ovulation. Whether P influences oocyte quality or maturation and follicle rupture independent of the midcycle gonadotropin surge was examined. Rhesus monkeys underwent controlled ovarian stimulation with recombinant human gonadotropins followed by a) experiment 1: an ovulatory bolus of hCG alone or with a steroid synthesis inhibitor (trilostane, TRL), or TRL + the progestin R5020; or b) no hCG, but rather sesame oil (vehicle), R5020, or dihydrotestosterone (DHT). In experiment 1, the majority of oocytes remained immature (65% +/- 20%) by 12 h post-hCG. However, the percentage of degenerating oocytes increased ($P < 0.05$) with TRL (42% +/- 22% vs. 0% controls), but was reduced ($P < 0.05$) by progestin replacement (15% +/- 7%). By 8 h post-hCG, the majority of oocytes in all three groups reached metaphase II (M). In experiment 2, no evidence of follicle rupture was observed in the vehicle, R5020, or DHT groups. Despite the absence of hCG, a significant ($P < 0.05$) percentage of oocytes resumed meiosis to metaphase I in R5020- (41 +/- 9) and DHT- (36 +/- 15) but not vehicle- (4 +/- 4) treated animals. Only oocytes from R5020-treated animals continued meiosis in vivo to MI. More ($P < 0.05$) oocytes fertilized in vitro with R5020 (40% than with vehicle (20%) or DHT (22%). Thus, P is unable to elicit ovulation in the absence of an ovulatory gonadotropin surge; however, P and/or androgens may prevent oocyte atresia and promote oocyte nuclear maturation in primate follicles.

10/3, AB/20
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15545876 PMID: 14967918
Interactions between the oocyte and surrounding somatic cells in follicular development: lessons from in vitro culture.
Senbon Shoichiro; Hirao Yuji; Miyano Takashi
Graduate School of Science and Technology, Faculty of Agriculture, Kobe University, Kobe 657-8501, Japan.
Journal of reproduction and development (Japan) Aug 2003, 49 (4) p259-69. ISSN: 0916-8818--Print Journal Code: 9438792
Publishing Model: Print
Document type: In Vitro; Journal Article; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Mammalian oogenesis occurs concomitantly with folliculogenesis in a coordinated manner in the ovaries. In vitro growth (IVG) culture systems of the oocytes have been developed as a new technology for utilizing incompetent oocytes in the ovary as a source of mature oocytes as well as for studying oogenesis, folliculogenesis, and oocyte-somatic cell

interactions. The results of IVG experiments have suggested that direct association of oocytes and surrounding granulosa cells supports oocyte viability and growth through the gap junctions, which are efficient conduits for low molecular weight substances. It has been revealed that granulosa cells metabolize some molecules which are in turn transported into the oocytes. IVG systems have also provided evidence that FSH promotes the development of follicles at secondary or later stages by its stimulation of proliferation and differentiation of granulosa cells, and perhaps by its anti-apoptotic effects. In addition, interactions between granulosa cell-derived KIT ligands and oocyte KIT receptors have been suggested as initiating oocyte growth and follicular development. Furthermore, recent findings suggest there are growth factors derived from oocytes such as GDF-9 and BMP-15. With such factors, oocytes participate in follicular development by regulating the differentiation of surrounding somatic cells. These bidirectional communications between oocytes and somatic cells are important for oocyte growth and follicular development. IVG systems should provide further information regarding oogenesis and folliculogenesis in the ovary.

10/3,AB/21
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15463661 PMID: 14615058
Synergistic effects of activin and FSH on hyperphosphorylation of Rb and G1/S transition in rat primary granulosa cells.
Ogawa Takuya; Yogo Keiichiro; Ishida Norihiro; Takeya Tatsuo
Graduate School of Biological Sciences, Nara Institute of Science and Technology, Ikoma, Nara 630-0101, Japan.
Molecular and cellular endocrinology (Ireland) Nov 28 2003, 210 (1-2) p31-8 ISSN 0303-7207--Print Journal Code: 7500844
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Activin is produced in mammalian ovarian follicles and is known to function as a paracrine as well as autocrine factor for folliculogenesis and oogenesis. We investigated the functional mechanism of activin using a hormone-supplemented serum-free culture system of granulosa cells isolated from diethylstilbestrol (DES)-primed 21-day-old rats. Recombinant human-activin A appeared to induce CycD2 and to act synergistically with FSH to promote G1/S transition and cell proliferation starting from 12h after stimulation accompanied by an increase of the hyperphosphorylated retinoblastoma protein (ppRb). Cells from unprimed rats gave similar results. FSH, in contrast, showed no CycD2-inducing activity, but turned out to modulate CycD2/cdk4 complex formation and enhance ppRb formation in conjunction with activin. These findings showed that the induction of CycD2 by activin and the synergistic effect of activin with FSH on ppRb formation play important roles in promoting G1/S transition in rat primary granulosa cells.

10/3,AB/22
DIALOG(R)File 155:MEDLINE(R)
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15075743 PMID: 12611607
Presence of LH receptor mRNA in granulosa cells as a potential marker of oocyte developmental competence and characterization of the bovine splicing isoforms.
Robert C; Gagne D; Lussier J G; Bousquet D; Barnes F L; Sirard M A
Centre de Recherche en Biologie de la Reproduction, Department of Animal Sciences, Laval University, QC, Canada G1K 7P4.
Reproduction (Cambridge, England) (England) Mar 2003, 125 (3) p437-46 ISSN 1470-1626--Print Journal Code: 100966036
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
As the expression of the LH receptor (LH-R) in granulosa cells is thought to be associated with later stages of folliculogenesis, this study was undertaken to evaluate the presence of LH-R mRNA as a suitable marker for developmental competence of oocytes. Granulosa cells and cumulus-oocyte complexes (COCs) were recovered from cows that had received ovarian stimulation. The COCs were subjected to embryo production procedures in vitro to assess the embryonic potential of the oocyte, and the corresponding granulosa cells were used to evaluate the presence of LH-R mRNA by RT-PCR. The presence of LH-R transcripts in granulosa cells is not a key characteristic of a follicle bearing a competent oocyte, although a higher proportion of oocytes reach the blastocyst stage when LH-R mRNA is detected in the granulosa cells. Different LH-R isoforms were cloned and sequence discrepancies

among six of the isoforms enabled the design of specific oligonucleotides to study the presence of the isoforms in different follicular cells. All LH-R transcripts studied and the 80 kDa protein product corresponding to the full length receptor were found in granulosa cells of small (< 4 mm) and large (> 5 mm) follicles. When the granulosa cells were cultured, the transcripts were downregulated by the culture conditions; downregulation was more acute in granulosa cells from small follicles. The addition of LH to the culture media enhanced LH-R mRNA downregulation. The presence of several LH-R transcript isoforms was tissue specific and in the theca cells LH-R mRNA was restricted mainly to cells from larger follicles. This finding indicates that the expression and the splicing of LH-R mRNA are regulated in a cell-specific and follicular size-specific manner.

10/3, AB/23
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14960506 PMID: 12543081
Morphological analyses of interleukin-8 effects on rat ovarian follicles at ovulation and luteinization in vivo.
Goto Junko; Suganuma Nobuhiko; Takata Kayoko; Kitamura Kimiya; Asahina Toshihiko; Kobayashi Hiroshi; Muranaka Yoshinori; Furuhashi Madoka; Kanayama Nbohiro
Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, Hamamatsu 431-3192, Japan.
Cytokine (United States) Nov 24 2002, 20 (4) p168-73, ISSN 1043-4666--Print Journal Code: 9005353
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The aim of the present study was to elucidate functions of the interleukin (IL)-8 at ovulation and luteinization in vivo. To compare the morphological differences between human chorionic gonadotropin (hCG) and IL-8 stimulation, scanning electron microscopy was employed to study rat ovarian vascular corrosion casts. Follicular growth and increased capillary vessel densities around the follicles were seen in vascular corrosion casts after IL-8 injection, similar to the result of hCG administration. This result indicated that exogenous IL-8 could play a role in the neovascularization during follicular development as an angiogenetic factor. Many fenestrations were observed in the vascular endothelium by hCG administration. In contrast, no fenestrations were observed with IL-8 injection, indicating that IL-8 may not be sufficient to increase the vascular permeability directly. Although germinal vesicle breakdown (GVBD) occurred at rates of 82% after the hCG injection, only 20% GVBD was observed after the IL-8 injection. The present study indicated that IL-8 might have important effects on rat follicles at ovulation and luteinization via vascularization in a similar manner to hCG. However, IL-8 was not effective on vascular permeability and oocyte maturation, which were different from hCG. Thus, we can conclude that IL-8 can participate in follicular development in part and may play important roles in ovulation and luteinization as one of some mediators induced by endogenous luteinizing hormone.

10/3, AB/24
DIALOG(R)File 155:MEDLINE(R)
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14522681 PMID: 11869185
Gap-junctional communication in mouse cumulus-oocyte complexes: implications for the mechanism of meiotic maturation.
Webb R J; Bains H; Crutttwell C; Carroll J
Department of Physiology, University College London, Gower Street, London WC1E 6BT, UK.
Reproduction (Cambridge, England) (England) Jan 2002, 123 (1) p41-52, ISSN 1470-1626--Print Journal Code: 100966036
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The mechanisms underlying the hormonal stimulation of meiotic maturation are not understood. The most prevalent hypothesis is that hormone-induced maturation is stimulated by an increase in the intracellular messengers, cAMP or Ca2+. This study investigated whether Ca2+ transients in somatic cells can lead to Ca2+ transients in the oocyte, and whether hormones that stimulate meiotic maturation of mouse oocytes in vitro and in vivo stimulate an increase in intracellular Ca2+. Of a range of potential agonists of Ca2+ release, ATP and UTP were the only agents that stimulated Ca2+ release in cumulus cells. ATP-induced Ca2+ release is from intracellular stores, as the response is not blocked

by chelation of extracellular Ca2+, but is inhibited by the Ca2+-ATPase inhibitor, thapsigargin. ATP and UTP are equipotent, consistent with the receptor being of the P2Y2 type. Confocal microscopy was used to show that ATP-induced Ca2+ release in cumulus cells leads to a Ca2+ increase in the oocyte. Inhibition of gap-junctional communication using carbenoxolone, as assayed by dye transfer, inhibited the diffusion of the Ca2+ signal from the cumulus cells to the oocyte. Thus, provided that a Ca2+ signal is generated in the somatic cells in response to maturation-inducing hormones, it is feasible that a Ca2+ transient is generated in the oocyte. However, FSH and EGF, both of which stimulate maturation in vitro, have no effect on Ca2+ in cumulus--oocyte complexes. Furthermore, LH, which leads to meiotic maturation in vivo, did not stimulate Ca2+ release in acutely isolated granulosa cells from preovulatory mouse follicles. These studies indicate that ATP may play a role in modulating ovarian function and that diffusion of Ca2+ signals through gap junctions may provide a means of communication between the somatic and germ cells of the ovarian follicle. However, our data are not consistent with a role for Ca2+-mediated communication in hormone-mediated induction of meiosis in mice.

10/3, AB/25
DIALOG(R)File 155:MEDLINE(R)
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14396432 PMID: 11787146
Embryo development, hormonal requirements and maternal responses during canine pregnancy.
Concannon P; Tsutsui T; Shille V
Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA.
Journal of reproduction and fertility. Supplement (England) 2001 , 57 p169-79, ISSN 0449-3087--Print Journal Code: 0225652
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The events of canine gestation appear to occur consistently among bitches relative to the time of the preovulatory LH surge. The interval from fertilization to the eight-cell stage was 5 days after insemination before oocyte maturation and only 3 days following insemination after oocyte maturation. Sixteen-cell embryos were observed at day 11 (day 0 = day of the LH surge) after either early or late insemination. Apparently, embryonic cleavage between the two-cell and 16-cell stages occurs more rapidly after fertilization of more mature oocytes. This finding, together with the narrow window for fertilization, may explain why the duration of gestation is similar whether mating occurs before or a few days after oocyte maturation. Observations also indicate that cessation of migration and final situating of embryos occurs between day 16 and day 20 and that uterine lumen vesicles are > 1 mm in diameter at days 17-19; vesicles are > 2 mm in diameter and elongated to 3-6 mm by days 20-22. Some blastocyst enlargement occurs between day 14 and day 20, and expansion inside lemon-shaped uterine vesicles prevents flushing of intact embryos from the uterus after day 20 or 21. Blastocysts can be enclosed in the zona pellucida as late as day 19 and loss of zona pellucida with further expansion occurs on days 19-20. Uterine swellings can be observed in vivo, albeit inconsistently, at days 21-22 at the time of embryo attachment, and even before invasion of the embryo into the endometrium. The uterine responses to embryo localization may be detected via uterine transillumination by day 21, even in the absence of gross swelling. Blastocysts remain unattached as late as days 21-22; invasion of placental trophectoderm occurs as early as day 22 and as late as day 23, and only 1-2 days before heartbeats are detected by sonography. Assay of canine relaxin by canine relaxin-specific radioimmunoassay detected increases in serum relaxin concentrations as early as days 26-30 and no earlier than the concurrent increase in serum prolactin concentrations at days 26-30; the increase in serum relaxin concentrations was also no earlier than increases in the concentrations of serum acute phase proteins, including fibrinogen. It is not known whether relaxin can stimulate prolactin secretion in dogs. When natural progesterone alone was provided by injection and subcutaneous implants before and after ovariectomy performed before implantation, implantation occurred normally, and pregnancy was maintained to term. The increase in prolactin was not different from that of control pregnancy, despite the absence of effective systemic concentrations of oestrogen, as observed by a typical castration response in LH and FSH. Lack of oestrogen may have compromised mammary development and lactation. Therefore, the pregnancy-associated increase in prolactin concentrations does not require an increase in or the presence of maternal oestrogen. These observations extend our knowledge of canine pregnancy and indicate several areas worthy of further investigation.

10/3, AB/26
DIALOG(R)File 155:MEDLINE(R)

14387930 PMID: 11771900
Effect of incubation temperature on in vitro maturation of porcine oocytes: nuclear maturation, fertilisation and developmental competence.
Abeydeera L R; Wang W H; Prather R S; Day B N
Department of Animal Sciences, University of Missouri, Columbia 65211, USA
Zygote (Cambridge, England) (England) Nov 2001, 9 (4) p331-7, ISSN 0967-1994--Print Journal Code: 9309124
Contract/Grant No.: HD 34588; HD; United States NICHD
Publishing Model: Print
Document type: Journal Article; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The present study examined the effect of low culture temperature during in vitro maturation (IVM) of pig oocytes on their nuclear maturation, fertilisation and subsequent embryo development. In experiment 1, oocytes were cultured at 35 or 39 degrees C for 44 h in modified tissue culture medium 199 supplemented with 10 ng/ml epidermal growth factor, 0.57 mM cysteine, 75 microg/ml potassium penicillin G, 50 microg/ml streptomycin sulphate, 0.5 microg/ml LH and 0.5 microg/ml FSH to examine the nuclear maturation status. In experiment 2, oocytes were cultured at 35 degrees C for 44 or 68 h and nuclear maturation was examined. In experiment 3, oocytes matured for 44 or 68 h at 39 degrees C and for 68 h at 35 degrees C were co-incubated with frozen-thawed spermatozoa for 5-6 h. Putative embryos were transferred into North Carolina State University (NCSU) 23 medium containing 0.4% bovine serum albumin. At 12 h after insemination, some oocytes were fixed to examine the fertilisation rate and the remaining embryos were examined at 48 and 144 h for cleavage and blastocyst formation rate, respectively. Compared with 39 degrees C, culture of oocytes at 35 degrees C for 44 h significantly ($p < 0.05$) reduced the metaphase II (MII) rate (79% vs 12%). However, extension of culture time to 68 h at 35 degrees C significantly increased ($p < 0.05$) the MII rate (7% vs 58%). In experiment 3, compared with other groups, fewer ($p < 0.05$) oocytes reached MII when cultured at 35 degrees C for 68 h (69-81% vs 49%). Extension of culture duration to 68 h at 39 degrees C stimulated spontaneous activation (28%) of oocytes. No difference in cleavage rates was observed among different groups. Compared with oocytes matured for 44 h at 39 degrees C (31%), the proportion of blastocysts obtained was low ($p < 0.05$) for oocytes matured at 35 degrees C (13%) or 39 degrees C (3%) for 68 h. The results indicate that lower culture temperature can delay nuclear maturation of pig oocytes. However, extension of culture time can stimulate nuclear maturation and these oocytes are capable of fertilisation and development to the blastocyst stage at moderate rates.

10/3,AB/27
DIALOG(R)File 155:MEDLINE(R)

14384008 PMID: 11750735
Follicle-stimulating hormone and advanced follicle development in the human.
Macklon N S; Fauser B C
Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands. macklon@yna.azr.nl
Archives of medical research (United States) Nov-Dec 2001, 32 (6) p595-600, ISSN 0188-4409--Print Journal Code: 9312706
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The great majority of human oocytes is destined to undergo atresia. Only follicles able to respond to stimulation by follicle-stimulating hormone (FSH) will enter the final stage of development and ovulate. While the role of FSH in early follicle development is unclear, late follicular development is FSH-dependent. FSH levels increase during the luteo-follicular transition and give rise to continued growth of a cohort of follicles. In the normo-ovulatory cycle, one follicle achieves a diameter of >8 mm and produces high concentrations of estradiol. In response to negative feedback from rising estradiol and inhibin levels, FSH levels fall in the late follicle phase. The dominant follicle has increased sensitivity to the falling FSH levels and continues growing. Follicles that initiate the latter stages of development after FSH levels begin to fall undergo atresia. The duration of this FSH window during which FSH levels are above the threshold required to stimulate ongoing development determines the number of follicles that can develop to the pre-ovulatory stage. Recognition of this concept has resulted in new approaches in ovulation induction treatment and ovarian hyperstimulation therapy for in vitro fertilization (IVF).

10/3, AB/28
DIALOG(R)File 155:MEDLINE(R)
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14270238 PMID: 11570966
Benefit of FSH priming of women with PCOS to the in vitro maturation procedure and the outcome: a randomized prospective study.
Mikkelsen A L; Lindenberg S
The Fertility Clinic, Herlev University Hospital, Institute for Human Reproduction, Fruebjergvej 3, DK-2100 Copenhagen, Denmark. alm@dadlnet.dk
Reproduction (Cambridge, England) (England) Oct 2001, 122 (4) p587-92, ISSN 1470-1626--Print Journal Code: 100966036
Publishing Model: Print
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The aim of this study was to determine whether the rates of in vitro oocyte maturation, fertilization and cleavage, as well as implantation rate and pregnancy rate, could be improved by low-dose priming with FSH in vivo before retrieval of immature oocytes in patients with polycystic ovary syndrome (PCOS). From March 1998 to June 2000, a total of 28 women underwent 36 completed treatment cycles, randomized sequentially in one of two groups. Women in group 1 (n = 12 cycles) received no stimulation and women in group 2 (n = 24 cycles) received 150 iu recombinant FSH day(-1) for 3 days, initiated on day 3 after menstruation. Aspiration was performed transvaginally between day 9 and day 17 in the unstimulated group and on day 8 or day 9 in the FSH-primed group after FSH deprivation for 2 or 3 days. All cumulus-enclosed oocytes of healthy appearance were matured in culture medium (TCM-199) in vitro for 28-36 h before intracytoplasmic sperm injection (ICSI). After oocyte retrieval the women were given oestradiol (6 mg day(-1)) and progesterone administration (300 mg day(-1)) was initiated 2 days later. Suitable embryos (maximum two embryos) were transferred on day 3 after ICSI. The percentage of oocytes reaching metaphase II was significantly higher (P < 0.05) in the FSH-primed group (59% 92/156) compared with the non-primed group (44% 36/81). There were no significant differences in the rates of oocyte fertilization and cleavage between these groups. No pregnancies were obtained in group 1 (0% 0/12), whereas seven clinical pregnancies were obtained in group 2 (29% 7/24) (P < 0.05). In group 2, 37 embryo transfers resulted in eight implantations (21.6%). Three healthy singleton children have been born at term, the remaining pregnancies ended with spontaneous abortions in the first trimester. These results indicate that priming with recombinant FSH before harvesting of immature oocytes from patients with PCOS may improve the maturational potential of the oocytes and the implantation rate of the cleaved embryos.

10/3, AB/29
DIALOG(R)File 155:MEDLINE(R)
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13556406 PMID: 10773386
Signal transduction mechanisms for LH in the cumulus-oocyte complex.
Mattioli M; Barboni B
Facolta di Medicina Veterinaria, Istituto di Fisiologia Veterinaria, Piano D'Accio, Teramo, Italy. barboni@fv.vet.unite.it
Molecular and cellular endocrinology (IRELAND) Mar 30 2000, 161 (1-2) p19-23, ISSN 0303-7207--Print Journal Code: 7500844
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The paper reviews recently described signalling mechanisms by which cumulus cells exposed to peak levels of gonadotropins, activate oocyte maturation. Cumulus cells react to LH with a prompt Ca raise which diffuses through gap junctions in a few minutes also into the oocyte where a local amplification system spreads the signal all over the cell. Few h later, still as a consequence of LH stimulation, cumulus cells undergo a progressive depolarisation of their plasma membrane potential. Due to the electric coupling with these cells the oocyte depolarises too and this open specific voltage-gated Ca channels responsible for a second wider and more sustained intracellular Ca rise. As a result of changes throughout maturation with a consequent modification of the size and charge of the molecules that can diffuse from one cell compartment to the other. This cell to cell interaction is further modified with cumulus expansion that leads to a progressive uncoupling of outer cumulus cells while the inner cell layer, corona radiata, remains in oocyte maturation by addressing to the oocyte nutrients and instructions in a well-orchestrated sequence. The identification of these mechanisms are a fundamental prerequisite for the development of in vitro systems suitable to produce oocytes matured in

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vitro with normal developmental competence.
? ds

Set       Items   Description
S1         1146   INFERTILITY AND (ADMINISTER OR ADMINISTRATION) AND (FSH OR
                   LH OR HCG)
S2          496   S1 AND PY<1998
S3          650   S1 NOT S2
S4            0   S3 AND TI=INFERTILITY
S5           69   S3 AND INFERTILITY/TI
S6           10   S5 AND (FSH OR LH OR HCG)/TI
S7            7   S3 AND FEMALE()INFERTILITY
S8            0   (STIMULATION OR STIMULATE)()OOGENESIS AND (FSH OR LH OR HC-
                   G)
S9           57   (STIMULATION OR STIMULATE) AND OOGENESIS AND (FSH OR LH OR -
                   HCG)
S10          29   S9 AND PY>1998
S11           0   T S10/3,AB/ALL
? s (stimulation or stimulate)and folliculogenesis and (fsh or lh or hcg)
          485197   STIMULATION
           79171   STIMULATE
            1353   FOLLICULOGENESIS
           24899   FSH
           39216   LH
           17552   HCG
S12          142   (STIMULATION OR STIMULATE) AND FOLLICULOGENESIS AND (FSH
                   OR LH OR HCG)
? s s12 and py.1998
             142   S12
               0   PY.1998
S13            0   S12 AND PY.1998
? s s12 and py>1998
             142   S12
         5491440   PY>1998
S14           75   S12 AND PY>1998
? s s14 not s10
              75   S14
              29   S10
S15           70   S14 NOT S10
? t s15/3,ab/all

 15/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
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26497691    PMID: 18353182
   Effects of high levels of glucose on the steroidogenesis and the
expression of adiponectin receptors in rat ovarian cells.
   Chabrolle Christine; Jeanpierre Eric; Tosca Lucie; Rame Christelle;
Dupont Joelle
   Unite de Physiologie de la Reproduction et des Comportements, Institut
National de la Recherche Agronomique, 37380 Nouzilly, France.
chabrolle@tours.inra.fr
   Reproductive biology and endocrinology - RB&E (England)  2008,  6
p11,  ISSN 1477-7827--Electronic  Journal Code: 101153627
   Publishing Model Electronic
   Document type: Journal Article
   Languages: ENGLISH
   Main Citation Owner: NLM
   Record type: MEDLINE; Completed
   BACKGROUND: Reproductive dysfunction in the diabetic female rat is
associated with altered folliculogenesis and steroidogenesis.
However, the molecular mechanisms involved in the reduction of steroid
production have not been described. Adiponectin is an adipocytokine that
has insulin-sensitizing actions including stimulation of glucose
uptake in muscle and suppression of glucose production in liver.
Adiponectin acts via two receptor isoforms - AdipoR1 and AdipoR2 - that are
regulated by hyperglycaemia and hyperinsulinaemia in liver and muscle. We
have recently identified AdipoR1 and AdipoR2 in rat ovary. However, their
regulation in ovaries of diabetic female rat remains to be elucidated.
METHODS: We incubated rat primary granulosa cells in vitro with high
concentrations of glucose (5 or 10 g/l) +/- FSH (10-8 M) or IGF-1
(10-8 M), and we studied the ovaries of streptozotocin-induced diabetic
rats (STZ) in vivo. The levels of oestradiol and progesterone in culture
medium and serum were measured by RIA. We used immunoblotting to assay key
steroidogenesis factors (3beta HSD, p450scc, p450 aromatase, StAR), and
adiponectin receptors and various elements of signalling pathways (MAPK
ERK1/2 and AMPK) in vivo and in vitro. We also determined cell
proliferation by [3H] thymidine incorporation. RESULTS: Glucose (5 or 10
g/l) impaired the in vitro production in rat granulosa cells of both
progesterone and oestradiol in the basal state and in response to FSH
and IGF-1 without affecting cell proliferation and viability. This was
associated with substantial reductions in the amounts of 3beta HSD,
p450scc, p450 aromatase and StAR proteins and MAPK ERK1/2 phosphorylation.
In contrast, glucose did not affect the abundance of AdipoR1 or AdipoR2
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proteins. In vivo, as expected, STZ treatment of rats caused hyperglycaemia and insulin, adiponectin and resistin deficiencies. Plasma progesterone and oestradiol levels were also reduced in STZ rats. However, the amounts of 3beta HSD and p450 aromatase were the same in STZ rat ovary and controls, and the amounts of StAR and p450scc were higher. Streptozotocin treatment did not affect adiponectin receptors in rat ovary but it increased AMPK phosphorylation without affecting MAPK ERK1/2 phosphorylation. CONCLUSION: High levels of glucose decrease progesterone and oestradiol production in primary rat granulosa cells and in STZ-treated rats. However, the mechanism that leads to reduced ovarian steroid production seems to be different. Furthermore, adiponectin receptors in ovarian cells are not regulated by glucose.

15/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
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26332558 PMID: 18339255
Anti-FSH antibodies associate with poor outcome of ovarian stimulation in IVF.
Haller Kadri; Salumets Andres; Uibo Raivo
Department of Immunology, Institute of General and Molecular Pathology, Centre of Molecular and Clinical Medicine, University of Tartu, Ravila Str. 19, Tartu 50411, Estonia. kadri.haller@ut.ee
Reproductive biomedicine online (England) Mar 2008, 16 (3) p350-5, ISSN 1472-6483--Print Journal Code: 101122473
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
FSH is required for spontaneous folliculogenesis and is widely used in ovarian stimulation in IVF. Previously, increased concentrations of antibodies against FSH (anti-FSH) have been demonstrated in infertile women. This study aimed to: (i) assess the possible association of anti-FSH with an adverse outcome of IVF with regard to clinical parameters characterizing the ovarian reserve; and (ii) compare serum and follicular fluid (FF) anti-FSH concentrations in relation to follicle size and endocrine markers. IVF patients (n = 182) subjected to gonadotrophin-releasing hormone-antagonist protocol were assessed for anti-FSH using enzyme-linked immunosorbent assay. Increased concentrations of serum anti-FSH immunoglobulin (Ig)G and IgA were associated with impaired ovarian stimulation outcome, with cut-off values <1.0 arbitrary units predicting poor ovarian response (<or=3 oocytes) (adjusted odds ratio for IgG = 6.95, P = 0.005 and IgA = 3.60, P = 0.039). FF anti-FSH IgG and IgA were positively associated with serum anti-FSH concentrations and FSH concentration in FF. Additionally, FF anti-FSH IgG increased with follicle growth (linear regression coefficient = 0.02, P = 0.022). Collectively, these data suggest that serum anti-FSH antibodies are associated with poor ovarian response to FSH stimulation in IVF, with anti-FSH IgA and IgG potentially exerting a local FSH antagonizing effect in maturing follicles.

15/3,AB/3
DIALOG(R)File 155:MEDLINE(R)
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26121174 PMID: 18084048
Effects of recombinant LH treatment on folliculogenesis and responsiveness to FSH stimulation.
Durnerin Cedrine I; Erb K; Fleming R; Hillier H; Hillier S G; Howles C M; Hugues J-N; Lass A; Lyall H; Rasmussen P; Thong J; Traynor I; Westergaard L ; Yates R
Reproductive Medicine Unit, Department of Gynaecology and Obstetrics, Jean Verdier Hospital, University Paris XIII, France.
Human reproduction (Oxford, England) (England) Feb 2008, 23 (2) p421-6, ISSN 1460-2350--Electronic Journal Code: 8701199
Publishing Model: Print-Electronic
Document type: Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: The role of LH in sensitizing antral follicles to FSH is unclear. LH is required for normal hormone production and normal oocyte and embryo development, but follicular responses to LH may depend upon the stage of development. Potential roles at the early follicular phase were explored in a clinical setting by employing a sequential approach to stimulation by recombinant human (r-h) LH followed by r-hFSH in women who were profoundly down-regulated by depo GnRH agonist. METHODS: We employed a multi-centre, prospective, randomized approach. Women (n = 146) were treated in along course

high-dose GnRH agonist (Decapeptyl, 4.2 mg s.c.) protocol and were randomized to receive r-hLH (Luveris, 300 IU/day) for a fixed 7 days, or no r-hLH treatment. This was followed by a standard r-hFSH stimulation regime (Gonal-F, 150 IU/day). Ultrasound and hormone assessments of responses were measured at the start of r-hLH treatment, on FSH stimulation Days 0 and 8 and at the time of hCG administration. RESULTS: The LH treatment was associated with increased small antral follicles prior to FSH stimulation (P = 0.007), and an increased yield of normally fertilized (2 PN) embryos (P = 0.03). There was no influence of the r-hLH pretreatment upon hormone profiles or ultrasound assessments during the FSH phase. Anti-mullerian hormone increased in both groups during the week prior to FSH stimulation (P = 0.002). CONCLUSIONS: This sequential approach to the use of r-hLH in standard IVF showed a possible modest clinical benefit. The results support other recent work exploring up-regulated androgen drive upon follicular metabolism indicating that clinical benefit may be obtainable after further practical explorations of the concept.

15/3, AB/4
DIALOG(R)File 155:MEDLINE(R)
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17854940 PMID: 17572411
Methylenetetrahydrofolate reductase (MTHFR) is associated with ovarian follicular activity.
Rosen Mitchell P; Shen Shehua; McCulloch Charles E; Rinaudo Paolo F; Cedars Marcelle I; Dobson Anthony T
Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, California 94115, USA.
Fertility and sterility (United States) Sep 2007, 88 (3) p632-8, ISSN 1556-5653--Electronic Journal Code: 0372772
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: Polymorphisms in the MTHFR gene have been associated with decreased cell division and apoptosis. This finding led us to evaluate whether MTHFR polymorphisms were associated with follicular growth within the ovary. More specifically, we investigated the effect of the two common polymorphisms, C677T and A1298C in our population of women undergoing ovarian stimulation. DESIGN: Prospective cohort study. SETTING: Academic medical center. PATIENT(S): Two hundred twenty-three women undergoing ovarian stimulation. INTERVENTION(S): The DNA from patients was genotyped at the MTHFR C677T and A1298C polymorphisms. MAIN OUTCOME MEASURE(S): Day 3 FSH, E(2), antral follicle count, amount of gonadotropin used, the number of follicles >13 mm, E(2) on the day of hCG administration, and oocyte number. RESULT(S): Women with the variant MTHFR 1298 C allele had significantly higher basal FSH levels, and after ovarian stimulation, produced fewer follicles >13 mm, had lower E(2) levels on the day of hCG administration, and required more ampules of gonadotropin hormone during treatment. Women with the variant MTHFR 677 T allele demonstrated no significant differences. CONCLUSION(S): The MTHFR A1298C polymorphism, but not the C677T polymorphism, is associated with higher basal FSH levels and may be a determinant of response to ovarian stimulation. These findings make a compelling case for the MTHFR A1298C polymorphism to modulate folliculogenesis.

15/3, AB/5
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17777223 PMID: 17540666
Allelic estrogen receptor 1 (ESR1) gene variants predict the outcome of ovarian stimulation in in vitro fertilization.
Altmae Signe; Haller Kadri; Peters Maire; Hovatta Outi; Stavreus-Evers Anneli; Karro Helle; Metspalu Andres; Salumets Andres
Department of Biotechnology, Institute of Molecular and Cell Biology, Estonian Genome Project, University of Tartu, Estonia, and Department of Clinical Science, Intervention and Technology, Karolinska University Hospital Huddinge, Stockholm, Sweden.
Molecular human reproduction (England) Aug 2007, 13 (8) p521-6, ISSN 1360-9947--Print Journal Code: 9513710
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The outcome of in vitro fertilization (IVF) depends substantially on the effectiveness of controlled ovarian hyperstimulation (COH) induced by administration of follicle-stimulating hormone (FSH). In COH, endogenously produced estrogens extend the action of FSH in

stimulating folliculogenesis. We determined the associations between genetic variations in estrogen receptor ESR1 and ESR2 genes and etiology of female infertility, and analysed the influence of these variations on COH outcome-the quantity and quality of oocytes retrieved. ESR1 PvuII T/C (rs2234693) and XbaI A/G (rs9340799) single-nucleotide polymorphisms (SNPs) and (TA)n microsatellite polymorphism as well as ESR2 RsaI G/A (rs1256049) SNP and (CA)n microsatellite polymorphism were genotyped in 159 IVF patients. The ovarian response to FSH was diminished in patients with endometriosis when compared to tubal factor infertility. ESR1 PvuII and XbaI as well as ESR2 RsaI SNPs were associated with the microsatellite length of the respective genes. Shorter ESR1 (TA)n was linked with a higher risk for unexplained infertility, whereas longer ESR1 (TA)n associated with PvuII*C allele were predictive of a better COH, but not clinical pregnancy outcome in an age-independent manner. These data suggest the variations in ESR1 gene, in addition to the age of a woman, may predict the COH outcome in IVF.

15/3, AB/6
DIALOG(R)File 155:MEDLINE(R)
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17629620 PMID: 17350962
Normalization of hormonal imbalances, ovarian follicular dynamics and metabolic effects in follitrophin receptor knockout mice.
Tiwari-Pandey Rashmi; Yang Yinzhi; Aravindakshan Jayaprakash; Sairam M Ram
Molecular Reproduction Research Laboratory, Clinical Research Institute of Montreal, (Affiliated to Universite de Montreal), Quebec, Canada.
Molecular human reproduction (England) May 2007, 13 (5) p287-97. ISSN 1360-9947--Print Journal Code: 9513710
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Genetically modified follitrophin receptor knockout female mice with total FSH-receptor (FSH-R) deletion are sterile and their combined estrogen deficiency-hyperandrogenemic status provides an experimental paradigm to study the effect of hormonal imbalances on ovarian function and metabolic alterations. Elevated LH levels causing hyperandrogenemia perturb normal folliculogenesis. To control diverse pathophysiology associated with hormonal imbalances, we investigated the effects of transplanting a single normal mouse ovary in young mutants. An intact FSH-R signalling system in the graft responded promptly to the up-regulated pituitary gonadotrophins circulating in the host mutant. Resumption of regular estrous cycles validated stimulation of uterine functions. Secretions from the viable functioning grafts partially corrected follicular abnormalities originally present in host ovaries. Stromal hyperplasia responsible for high ovarian LH-receptor and key enzymes in host thecal/interstitial complex and hyperandrogenemia was reduced in host ovaries. Increases in plasma estradiol and reduced LH and free testosterone re-established the negative-feedback system. Reduced android obesity and activation of mammary glands indicated the combined beneficial effects of normalized steroid hormones on target organs. These data provide evidence that ovarian transplantation in mutants corrects estrogen loss and hyperandrogenemia. However, correction of hormonal imbalances is not sufficient to fully restore effects of FSH-R loss in host granulosa cells.

15/3, AB/7
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17397747 PMID: 17146736
Is estradiol mandatory for an adequate follicular and embryo development? A mouse model using aromatase inhibitor (anastrozole).
Fatum Muhammad; Gyo Yi; Diana Prus; Laufer Neri; Simon Alex
Department of Obstetrics and Gynecology, Hadassah University Hospital, Ein Kerem, P.O. Box 12000, Jerusalem 91120, Israel. fatum@md.huji.ac.il
Journal of assisted reproduction and genetics (United States) Nov-Dec 2006, 23 (11-12) p407-12, ISSN 1058-0468--Print Journal Code: 9206495
Publishing Model: Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: Although high levels of estradiol are found in the follicular fluid, little is known about its necessity for adequate follicular growth, oocyte maturation and embryo development. Arimidex (anastrozole) is a potent aromatase inhibitor capable to induce an in-vivo milieu deprived of estradiol. This study uses a mouse model applying Arimidex to create an in-vivo system lacking of estradiol, in order to explore whether this

gonadal steroid hormone is mandatory for folliculogenesis followed by normal fertilization and embryo development. METHODS: Experiment 1: Immature C57 Black female mice, aged 3-4 weeks were superovulated by 5 IU PMSG given intraperitoneally. A study group (9 mice) was concomitantly injected with 0.1 mg of Arimidex intraperitoneally given the morning day before PMSG, the morning day of PMSG injection and the following two days. The control group (8 mice) was similarly injected with normal saline. Estradiol (E2) and progesterone (P) serum levels were tested 48 hours after PMSG and the ovaries of each mouse blindly examined by a pathologist to evaluate follicular development. Experiment 2: 48 h after PMSG superovulation, hCG (7.5 IU) was injected intraperitoneally, followed by mating. The study group was treated with Arimidex 0.1 mg intraperitoneally daily from a day prior to PMSG injection to the day of sacrifice. The control group was treated similarly by normal saline. Forty-two hours after mating blood was withdrawn for E2 and P levels followed by tubal dissection. Embryos of 2-4 cells were cultured in-vitro and the development to the morula, blastocyst and hatching blastocyst stages were examined 24, 42, and 48 h later. RESULTS: Experiment 1: A significant reduction of E2 levels was achieved in the Arimidex group in comparison to control group (126.3+/-104.8 and 1910+/-960 pmol/L, respectively; p <= 0.0001). Nevertheless, the two groups did not differ by the mean number of follicles (27+/-9.5 and 30.4+/-13.0) or the distribution for antral (65% and 68.4%) and pre-antral (35% and 31.6%) follicles, respectively. Experiment 2: The reduction of estradiol during follicular phase did not hamper follicular development, in-vivo fertilization and in-vitro embryo development. Similar rates of embryo development to the morula stage (90.6% and 86%), blastocyst stage (86% and 89%) and hatching blastocyst (81% and 78%) were achieved in the Arimidex group and the control group, respectively. CONCLUSIONS: Adequate folliculogenesis is independent of estrogen but is conditioned on gonadotropin stimulation. Moreover, depletion of estradiol in the vicinity of the oocyte did not impair its developmental potential, including its fertilization and development into morulae, blastocysts and hatching blastocysts.

15/3, AB/8
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17317006 PMID: 16825293
Interleukin-1alpha-induced chemokines in mouse granulosa cells: impact on keratinocyte chemoattractant chemokine, a CXC subfamily.
Son Deok-Soo; Roby Katherine F
Center of Reproductive Sciences, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, Kansas 66160-7417, USA. dson@kumc.edu
Molecular endocrinology (Baltimore, Md.) (United States) Nov 2006, 20 (11) p2999-3013, ISSN 0888-8809--Print Journal Code: 8801431
Contract/Grant No.: P20 RR016475: RR, United States NCRR
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, N.I.H., Extramural
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
IL-1 is well known to be involved in the immune system and have a role in ovarian inflammation as well as exhibiting inhibitory effects on steroidogenesis and folliculogenesis. Because multiple aspects of ovarian function have also been shown to involve cytokine/chemokine networks, IL-1alpha-induced chemokine gene expression in mouse granulosa cells was investigated. Granulosa cells from immature mice at 28 d of age were cultured with IL-1alpha (10 ng/ml). IL-1alpha induced abundantly and specifically keratinocyte chemoattractant (KC) chemokine, a CXC subfamily. KC chemokine mRNA and protein were increased 1-2 h after IL-1alpha and then gradually decreased. The KC promoter (-701/+30) containing three nuclear factor (NF)-kappaB sites was fully responsive to IL-1alpha, whereas deletions and mutants of the NF-kappaB sites lowered the responsiveness to IL-1alpha. The proximal NF-kappaB site (-69/-59) played a critical role in regulating IL-1alpha-induced KC chemokine promoter activity. Overexpression of the inhibitor of NF-kappaB (IkappaB) blocked KC promoter activity induced by IL-1alpha, whereas overexpression of p65, a component of NF-kappaB, increased promoter activity and mRNA of KC chemokine. In addition, FSH did not affect NF-kappaB signaling or IL-1alpha-induced KC chemokine promoter activity. Within 1-3 h after ip injection of lipopolysaccharide (100 mug/mouse), a product known to stimulate release of IL-1, KC chemokine was localized in the ovary to granulosa cells as well as the thecal-interstitial layer. The results of this study indicate that KC gene is a chemokine induced acutely by IL-1alpha via NF-kappaB signaling in mouse granulosa cells.

15/3, AB/9
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17176797 PMID: 16827936

Identification of differential gene expression in in vitro FSH-treated pig granulosa cells using suppression subtractive hybridization.
Bonnet A; Frappart P O; Dehais P; Tosser-Klopp G; Hatey F
INRA, laboratoire de Genetique cellulaire, BP52627 chemin de borde rouge, 31326 Castanet cedex, France. abonnet@toulouse.inra.fr
Reproductive biology and endocrinology - RB&E (England) 2006, 4 p35, ISSN 1477-7827--Electronic Journal Code: 101153627
Publishing Model Electronic
Document type: Comparative Study; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
FSH, which binds to specific receptors on granulosa cells in mammals, plays a key role in folliculogenesis. Its biological activity involves stimulation of intercellular communication and upregulation of steroidogenesis, but the entire spectrum of the genes regulated by FSH has yet to be fully characterized. In order to find new regulated transcripts, however rare, we have used a Suppression Subtractive Hybridization approach (SSH) on pig granulosa cells in primary culture treated or not with FSH. Two SSH libraries were generated and 76 clones were sequenced after selection by differential screening. Sixty four different sequences were identified, including 3 novel sequences. Experiments demonstrated the presence of 25 regulated transcripts. A gene ontology analysis of these 25 genes revealed (1) catalytic; (2) transport; (3) signal transducer; (4) binding; (5) anti-oxidant and (6) structural activities. These findings may deepen our understanding of FSH's effects. Particularly, they suggest that FSH is involved in the modulation of peroxidase activity and remodelling of chromatin.

15/3, AB/10
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17171069 PMID: 16601008
Comparison of follicular fluid IGF-I, IGF-II, IGFBP-3, IGFBP-4 and PAPP-A concentrations and their ratios between GnRH agonist and GnRH antagonist protocols for controlled ovarian stimulation in IVF-embryo transfer patients.
Choi Young Sik; Ku Seung-Yup; Jee Byung-Chul; Suh Chang-Suk; Choi Young Min; Kim Jung Gu; Moon Shin Yong; Kim Seok Hyun
Department of Obstetrics and Gynecology, College of Medicine, Seoul National University, Korea.
Human reproduction (Oxford, England) (England) Aug 2006, 21 (8) p2015-21, ISSN 0268-1161--Print Journal Code: 8701199
Publishing Model Print-Electronic
Document type: Clinical Trial; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: Insulin-like growth factors (IGF) and their binding proteins (IGFBP) play a major role in the autocrine and paracrine regulation of folliculogenesis. This is the first study that has compared follicular fluid (FF) IGF-I, IGF-II, IGFBP-3, IGFBP-4 and pregnancy-associated plasma protein (PAPP)-A concentrations, and their ratios, to investigate whether there was any difference in the intrafollicular microenvironment between the GnRH agonist (GnRHa) and antagonist (GnRHant) protocols for controlled ovarian stimulation (COS). METHODS: A total of 68 IVF cycles were included in this study; two groups were studied: GnRHa long protocol group (n = 36) and the flexible GnRHant multiple-dose protocol group (n = 32). FF was obtained from dominant follicles during oocyte retrieval and stored at -70 degrees C until assayed. IGF-I, IGF-II and IGFBP-3 concentrations were measured by radioimmunoassay and IGFBP-4 and PAPP-A by enzyme-linked immunosorbent assay. RESULTS: The duration of COS was significantly longer, and total dose of gonadotrophins used, serum estradiol (E(2)) levels on hCG day and the number of oocytes retrieved were significantly higher in the GnRHa long protocol group. The concentrations of FF IGF-II and IGFBP-4 were significantly higher, and the ratio of IGF-I/IGFBP-4 was significantly lower in the GnRHa long protocol group. Serum E(2) levels per mature follicle were not different between the two groups. CONCLUSIONS: Our data may indicate a difference of intrafollicular microenvironment between cycles using GnRHa long protocols and those using GnRHant protocols. However, the difference in microenvironment does not appear to result in a difference in clinical outcome.

15/3, AB/11
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17147925 PMID: 16625003
Transcriptional regulation of cyclin D2 by the PKA pathway and inducible cAMP early repressor in granulosa cells.

Muniz Luis C; Yehia Ghassan; Memin Elisabeth; Ratnakar Pillarisetty V A L ; Molina Carlos A
Department of Biochemistry and Molecular Biology and Graduate School of Biomedical Sciences, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, New Jersey 07103, USA.
Biology of reproduction (United States) Aug 2006, 75 (2) p279-88, ISSN 0006-3363--Print Journal Code: 0207224
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Publishing Model Print-Electronic
Document type: Journal Article; Research Support, N.I.H., Extramural
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Cyclin D2 (Ccnd2) is an essential gene for folliculogenesis, as null mutation in mice impairs granulosa cell proliferation in response to FSH. Ccnd2 mRNA is induced during the estrus cycle by FSH and is rapidly inhibited by LH. Yet, the responsive elements and transcription factors accounting for the gene expression of cyclin D2 in the ovary have not been fully characterized. Using primary cultures of rat granulosa cells and immortalized mouse granulosa cells, we demonstrate a mechanism for the regulation of cyclin D2 at the level of transcription via a PKA-dependent signaling mechanism. The promoter activity of cyclin D2 was shown to be induced by FSH and the catalytic alpha subunit of PKA (PRKACA), and this activity was repressible by inducible cAMP early repressor (ICER), a cAMP response element (CRE) modulator isoform. In silico analysis of the mouse, rat, and human cyclin D2 promoters identified two CRE-binding protein sites, a conserved proximal element and a less conserved distal element relative to the translation start site. The mutation on the proximal element drastically decreases the effects of PRKACA and ICER on the promoter activity, whereas the mutation on the distal element did not contribute to the decrease in the promoter activity. Electrophoretic mobility shift assays and deoxyribonuclease footprint analysis confirmed ICER binding to the proximal element, and chromatin immunoprecipitation analysis demonstrated the occurrence of this binding in vivo. These results showed a CRE within the upstream region of Ccnd2 that is (at least partly) implicated in the stimulation and repression of cyclin D2 transcription. Finally, our data suggest that ICER involvement in the regulation of granulosa cell proliferation as overexpression of ICER results in the inhibition of PRKACA-induced DNA synthesis.

15/3, AB/12
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17125187 PMID: 16824444
A review of the effects of supplementary nutrition in the ewe on the concentrations of reproductive and metabolic hormones and the mechanisms that regulate folliculogenesis and ovulation rate.
Scaramuzzi Rex J; Campbell Bruce K; Downing Jeff A; Kendall Nigel R; Khalid Muhammad; Munoz-Gutierrez Minerva; Somchit Anongnart
Department of Veterinary Basic Sciences, Royal Veterinary College, North Mymms, Hertfordshire, UK. rscara@vvc.ac.uk
Reproduction, nutrition, development (France) Jul-Aug 2006, 46 (4) p339-54, ISSN 0926-5287--Print Journal Code: 8913069
Publishing Model Print-Electronic
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
This paper discusses the phenomenon of nutritional flushing in ewes whereby increased nutrition stimulates folliculogenesis and ovulation rate. In addition the paper reviews recent findings on the effects of increased levels of nutrition on the blood concentrations of reproductive and metabolic hormones in the ewe and some of the intraovarian changes that take place in response to nutritional stimulation. Finally, in the paper, we propose a model of the physiological mechanism for the nutritional stimulation of folliculogenesis and we review how closely the model fits recent published and unpublished evidence examining the mechanism of flushing. Nutritional stimulation alters the blood concentrations of some metabolic hormones. By using short-term models of nutritional flushing, we have shown that as the blood concentrations of insulin and leptin increase that of growth hormone decreases while that of IGF-I appears unaffected by the nutritional flushing. Nutritional flushing also alters the blood concentrations of some reproductive hormones. Again, using the same model, we have shown that there is a transient increase in FSH and a decrease in oestradiol concentrations in the blood. The changes in oestradiol are particularly evident in the follicular phase of the oestrous cycle. In the ovary, the effect of nutrition is to stimulate folliculogenesis. These changes are associated with intra-follicular alterations in the insulin-glucose, IGF and leptin metabolic systems. The stimulation of these intra-follicular systems leads to a suppression in follicular oestradiol production. The consequence of these direct actions on the follicle is a reduced negative feedback to

the hypothalamic-pituitary system and increased FSH secretion that leads to a stimulation of folliculogenesis.

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17108843 PMID: 16474210
PKA implicated in the phosphorylation of Cx43 induced by stimulation with FSH in rat granulosa cells.
Yogo Keiichiro; Ogawa Takuya; Akiyama Motofusa; Ishida-Kitagawa Norihiro; Sasada Hiroshi; Sato Eimei; Takeya Tatsuo
Graduate School of Biological Sciences, Nara Institute of Science and Technology, Japan. ke-yogo@bs.naist.jp
Journal of reproduction and development (Japan) Jun 2006, 52 (3) p321-8, ISSN 0916-8818--Print Journal Code: 9438792
Publishing Model: Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Connexin 43 (Cx43)-mediated gap junctional communication in granulosa cells is crucial for germline development and postnatal folliculogenesis. We previously showed that follicle-stimulating hormone (FSH) promoted phosphorylation of Cx43 in rat primary granulosa cells. We further identified Ser365, Ser368, Ser369, and Ser373 in the carboxy-terminal tail as the major sites of phosphorylation by FSH and found that the phosphorylation of these residues was essential for channel activity. In this study, we investigated the protein kinase(s) responsible for FSH-induced phosphorylation. H89, a cyclic AMP-dependent protein kinase (PKA) inhibitor, inhibited FSH-induced phosphorylation both in vivo and in vitro, whereas PD98059, a mitogen-activated protein kinase kinase (MEK) inhibitor, had little effect on the phosphorylation level. Ca2+-dependent protein kinase (PKC) appeared to negatively regulate phosphorylation. Phosphopeptide mapping with or without H89 treatment indicated that PKA could be responsible for phosphorylation of the four serine residues. In addition, the purified catalytic subunit of PKA could phosphorylate the recombinant C-terminal region of Cx43, but not the variant in which all four serine residues were substituted with alanine. These results suggest that FSH positively regulates Cx43-mediated channel formation and activity through phosphorylation of specific sites by PKA.

15/3, AB/14
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17101085 PMID: 16792843
FSH and folliculogenesis: from physiology to ovarian stimulation.
Vegetti Walter; Alagna Federica
Infertility Unit, Fondazione I.R.C.C.S. Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan, Italy. waltervegetti@yahoo.it
Reproductive biomedicine online (England) Jun 2006, 12 (6) p684-94, ISSN 1472-6483--Print Journal Code: 101122473
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
FSH is a glycoprotein hormone consisting of two peptide subunits. The role of FSH in folliculogenesis is well known: to stimulate the formation of a large pre-ovulatory follicle that, because of its FSH-dependent maturation, is capable of ovulation and forming a corpus luteum in response to the mid-cycle surge of LH. FSH is widely used in ovarian stimulation for assisted reproduction techniques. Ovarian stimulation protocols combine the use of human menopausal gonadotrophin, urinary FSH or recombinant FSH with gonadotrophin-releasing hormone (GnRH) agonists or antagonists in order to increase oocyte number and to avoid premature LH surge. Recently, the availability of recombinant LH has permitted new stimulation protocols, combining recombinant FSH, recombinant LH and GnRH antagonists. Due to the limitations of the new Italian law in terms of the number of oocytes that can be fertilized, protocols with a softer ovarian stimulation are now considered, reducing risk of ovarian hyperstimulation syndrome, multiple pregnancies and emotional and physical burdens on the patients. Long-acting FSH preparations are also under clinical study. Knowledge of the stereochemical three-dimensional structure of FSH and its receptor will allow the study of new non-peptide orally administered molecules that fit the FSH receptors.

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17098842 PMID: 16790105
Outlook: who needs LH in ovarian stimulation?
Alviggi C; Clarizia R; Mollo A; Ranieri A; De Placido G
Dipartimento di Scienze Ostetriche Ginecologiche Urologiche e Medicina della Riproduzione-Universita degli Studi di Napoli 'Federico II', Naples, Italy. alviggi@unina.it
Reproductive biomedicine online (England) May 2006, 12 (5) p599-607, ISSN 1472-6483--Print Journal Code: 101122473
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
LH plays a key role in the intermediate-late phases of folliculogenesis. Although ovarian stimulation is efficiently achieved in most cases by the administration of exogenous FSH alone, specific subgroups of women may benefit from LH activity supplementation during ovarian stimulation. Some authors have found improved outcome with LH activity supplementation in advanced reproductive age women. Experience suggests that in about 10-12% of young normogonadotrophic patients treated with a gonadotrophin-releasing hormone agonist (GnRH-a) long protocol plus recombinant FSH human (r-hFSH), a 'steady response' is observed. In this subgroup of women, a higher number of oocytes is retrieved when daily LH activity supplementation is given from stimulation day 8, if compared with the standard FSH dose increase. Another subgroup of patients who may benefit from LH activity supplementation are those at risk for poor ovarian response treated with GnRH antagonist. Recent data demonstrate that in these women, when GnRH is administered in a flexible protocol, the concomitant addition of recombinant human LH improves the number of mature oocytes retrieved, when compared with the standard GnRH-a flare-up protocol. Thus, well calibrated LH administration improves the ovarian outcome in patients >35 years, in those showing an initial abnormal ovarian response to r-hFSH monotherapy, and in 'low prognosis' women treated with GnRH antagonists.

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17015954 PMID: 16540466
Allosteric activation of the follicle-stimulating hormone (FSH) receptor by selective, nonpeptide agonists.
Yanofsky Stephen D; Shen Emily S; Holden Frank; Whitehorn Erik; Aguilar Barbara; Tate Emily; Holmes Christopher P; Scheuerman Randall; MacLean Derek; Wu May M; Frail Donald E; Lopez Francisco J; Winneker Richard; Arey Brian J; Barrett Ronald W
Affymax, Inc., Palo Alto, California 94304, USA. syanofsky@bcglobal.net
Journal of biological chemistry (United States) May 12 2006, 281 (19) p13226-33, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model: Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The pituitary glycoprotein hormones, luteinizing hormone and follicle-stimulating hormone (FSH), act through their cognate receptors to initiate a series of coordinated physiological events that results in germ cell maturation. Given the importance of FSH in regulating folliculogenesis and fertility, the development of FSH mimetics has been sought to treat infertility. Currently, purified and recombinant human FSH are the only FSH receptor (FSH-R) agonists available for infertility treatment. By screening unbiased combinatorial chemistry libraries, using a cAMP-responsive luciferase reporter assay, we discovered thiazolidinone agonists (EC50's = 20 microm) of the human FSH-R. Subsequent analog library screening and parallel synthesis optimization resulted in the identification of a potent agonist (EC50 = 2 nm) with full efficacy compared with FSH that was FSH-R-selective and -dependent. The compound mediated progesterone production in Y1 cells transfected with the human FSH-R (EC50 = 980 nm) and estradiol production from primary rat ovarian granulosa cells (EC50 = 10.5 nm). This and related compounds did not compete with FSH for binding to the FSH-R. Use of human FSH/thyroid-stimulating hormone (TSH) receptor chimeras suggested a novel mechanism for receptor activation through a binding site independent of the natural hormone binding site. This study is the first report of a high affinity small molecule agonist that activates a glycoprotein hormone receptor through an allosteric mechanism. The small molecule FSH receptor agonists described here could lead to an oral alternative to the current parenteral FSH treatments used clinically to induce ovarian

stimulation for both in vivo and in vitro fertilization therapy.

15/3, AB/17
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16971508 PMID: 16556681
Transcriptome analysis of FSH and FSH variant stimulation in granulosa cells from IVM patients reveals novel regulated genes.
Perlman S; Bouquin T; van den Hazel B; Jensen T H; Scharrbye H T; Knudsen S; Ockels J S
Maxygen, Horsholm Technical University of Denmark, Lyngby.
Molecular human reproduction (England) Mar 2006, 12 (3) p135-44, ISSN 1360-9947--Print Journal Code: 9513710
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
FSH is crucial for oocyte maturation and fertility and is the main component in infertility treatment in assisted reproduction. The granulosa cells expressing the FSH receptor interact with the oocyte and provide nourishing substrates controlling the oocyte maturation. Thus, transcriptome analysis of granulosa cells stimulated by FSH is of major importance in understanding the communication between oocytes and granulosa cells. In this study, gene expression profiles were assessed in human granulosa cells from normal cycling in vitro maturation (IVM) patients using oligonucleotide gene chips. Granulosa cells were stimulated for 2 h with either FSH or a previously generated glycosylated FSH variant (FSH1208) that exhibited increased in vivo activity because of prolonged half-life. The analysis identified 74 significantly FSH/FSH1208 regulated genes. Amongst these were well known FSH regulated genes as well as genes not previously described to be important in the FSH signalling pathway. These novel FSH-regulated genes include transcription factors [cAMP responsive element modulator (CREM)/inducible cAMP early repressors (ICER), GATA 6, ZFN 361, Bcl11a, CTED1 and TCF 8] and other regulatory proteins and enzymes (IGF-BP3, syntaxin and PCK1) possibly important for oocyte/granulosa cell interaction and function. Array data were validated for 13 genes by northern blots or RT-PCR. Furthermore, significant differences in gene regulation were detected between the two FSH analogs. This work uncovers novel data important for understanding the folliculogenesis. Furthermore, the results suggest that FSH1208 has a gene expression profile like FSH and thus, in the light of known prolonged in vivo activity, might be a candidate for improved infertility treatment.

15/3, AB/18
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16880762 PMID: 16478591
Exploiting LH in ovarian stimulation.
Alviggi C; Mollo A; Clarizia R; De Placido G
Dipartimento di Scienze Ostetriche Ginecologiche Urologiche e Medicina della Riproduzione-Universita degli Studi di Napoli Federico II, via S. Pansini 5, 80131, Naples, Italy. alviggi@amina.it
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Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
During intermediate-late phases of human folliculogenesis, LH plays a key role in promoting steroidogenesis and growth of the leading follicle. Ovarian stimulation for assisted reproduction techniques usually consists of administering exogenous FSH in a low LH environment. Although an impairment in LH-dependent paracrine activities would be expected, multiple follicular growth is efficiently achieved in almost all patients. Thus, there appears to be a discrepancy between classical folliculogenesis models and data from IVF. This study examines the 'interface' between basic endocrinological and clinical evidence, in an attempt to answer two questions: is there an LH therapeutic window, and if there is, how can this be exploited in the practice of assisted reproduction? It also reviews the evidence that specific subgroups of women may benefit from LH supplementation during ovarian stimulation.

15/3, AB/19
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16684146 PMID: 16274596
LH improves early follicular recruitment in women over 38 years old.
Gomez-Palomares J L; Acevedo-Martin B; Andres L; Ricciarelli E; Hernandez E R
Clinica de Medicina de la Reproduccion y Ginecologia 'FIVMadrid', C/Marques de Urquijo 26, 28008 Madrid, Spain.
Reproductive biomedicine online (England) Oct 2005, 11 (4) p409-14. ISSN 1472-6483--Print Journal Code: 101122473
Publishing Model Print; Erratum in Reprod Biomed Online. 2006 Jan; 12(1) 132
Document type: Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Although the capacity of recombinant FSH alone to induce folliculogenesis is undisputed, many believe that follicular recruitment in women over 38 years old could be improved by supplementing rFSH with human menopausal gonadotrophin (HMG). The present study sought to determine whether recombinant LH could reproduce the effect of HMG in women over 38 years during ovulation induction. Fifty-eight patients received rFSH (225 IU/day) supplemented with one ampoule of HMG (75 IU of FSH/75 IU of LH/hCG per day) for 5 days. Another 36 patients received rFSH (300 IU/day) supplemented with one ampoule of rLH (75 IU/day), also for 5 days. Both groups of patients received similar amounts of rFSH (1500 IU), LH/hCG (375 IU) and rLH (375 IU) and recruited a similar number of follicles as counted on day 6 (4.07 +/- 3.1 in the HMG group versus 3.7 +/- 3.2 in the LH group respectively) or on the day that human chorionic gonadotrophin (hCG) was indicated (6.5 +/- 2.7 versus 5.8 +/- 2.5 respectively). Ovarian stimulation was shorter, but not significantly so, in the group of patients receiving rFSH + HMG (10.1 +/- 1.7 days) than in the group of patients treated with rFSH +/- rLH (12 +/- 1.8 days). Significantly more MII oocytes were seen in the group treated with rFSH + rLH than in the group treated with rFSH + HMG (93.1 versus 75.3%, P < 0.05). With respect to pregnancy rates, 14/54 (26%) patients receiving rFSH + HMG and 16/34 (47%) patients receiving rFSH + rLH had a positive serum hCG. No significant difference in the number of miscarriages was observed between the two groups. In conclusion, the present results seem to indicate that rLH could be the HMG component that aids early follicular recruitment.

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16618041 PMID: 16195824
Differences in serum LH and FSH levels using depot or daily GnRH agonists in controlled ovarian stimulation: influence on ovarian response and outcome of ART.
Sonntag Barbara; Kiesel Ludwig; Nieschlag Eberhard; Behre Hermann M
Assisted Reproduction Unit, Department of Obstetrics and Gynaecology, Munster, Germany.
Journal of assisted reproduction and genetics (United States) Aug 2005, 22 (7-8) p277-83, ISSN 1058-0468--Print Journal Code: 9206495
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Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
PURPOSE: To study effects of endogenous LH levels on ovarian response and outcome in ART cycles a controlled study was performed with two patient groups differing in the intensity of pituitary downregulation. METHODS: Group I (n = 27) received 3.75 mg of the GnRH agonist triptorelin acetate depot, group II (n = 54) was given 0.1 mg triptorelin acetate daily, followed by ovarian stimulation with recombinant FSH. RESULTS: After downregulation serum LH and FSH levels were significantly lower in group I. Patients of group I needed significantly higher FSH doses to achieve comparable levels of serum estradiol and preovulatory follicles. The number of retrieved oocytes and transferable embryos was lower in group I. CONCLUSION: Patients with profound endogenous LH suppression by depot GnRH agonists show higher FSH stimulation dose requirements and lower oocyte number and fertilization rate, indicating a need for minimal LH activity in folliculogenesis and oocyte development.

15/3,AB/21
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16611236 PMID: 15941853
Knockout of luteinizing hormone receptor abolishes the effects of

follicle-stimulating hormone on preovulatory maturation and ovulation of mouse graafian follicles.
Pakarainen Tomi; Zhang Fu-Ping; Nurmi Laura; Poutanen Matti; Huhtaniemi Ilpo
Department of Physiology, University of Turku, Fin-20500 Turku, Finland.
Molecular endocrinology (Baltimore, Md.) (United States) Oct 2005, 19 (10) p2591-602, ISSN 0888-8809--Print Journal Code: 8801431;
Contract/Grant No.: United Kingdom Wellcome Trust
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
It is considered a dogma that a secretory peak of LH is indispensable as the trigger of ovulation. However, earlier studies on hypophysectomized rodents have shown that stimulation with recombinant FSH, devoid of any LH activity, is able to boost the final stages of follicular maturation and trigger ovulation. As the expression of ovarian LH receptors (LHRs) still persists after hypophysectomy, such studies cannot totally exclude the possibility that LHR activation is involved in the apparently pure FSH effects. To revisit this question, we analyzed in LHR knockout (LuRKO) mice the progression of folliculogenesis and induction of ovulation by human chorionic gonadotropin and human recombinant FSH treatments. The results provide clear evidence that follicular development and ovulation could not be induced by high doses of FSH in the absence of LHR expression. Ovarian histology and oocyte analyses indicated that follicular maturation did not advance in LuRKO mice beyond the antral follicle stage. Neither were ovulations detected in LuRKO ovaries after any of the gonadotropin treatments. The ovarian resistance to FSH treatment in the absence of LHR was confirmed by real-time RT-PCR and immunohistochemical analyses of a number of gonadotropin-dependent genes, which only responded to the treatments in wild-type control mice. Negative findings were not altered by estradiol priming preceding the gonadotropin stimulations. Hence, the present study shows that, in addition to ovulation, the expression of LHR is essential for follicular maturation in the progression from antral to preovulatory stage.

15/3,AB/22
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16600140 PMID: 15972887
Androgens augment the mitogenic effects of oocyte-secreted factors and growth differentiation factor 9 on porcine granulosa cells.
Hickey T E; Marrocco D L; Amato F; Ritter L J; Norman R J; Gilchrist R B; Armstrong D T
Research Centre for Reproductive Health, Department of Obstetrics and Gynaecology, University of Adelaide, Woodville, South Australia. theresa.hickey@adelaide.edu.au
Biology of reproduction (United States) Oct 2005, 73 (4) p825-32, ISSN 0006-3363--Print Journal Code: 0207224
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
In this study, we test the hypothesis that the growth-promoting action of androgens on granulosa cells requires paracrine signaling from the oocyte. Mural granulosa cells (MGCs) from small antral (1-3 mm) prepubertal pig follicles were cultured in the presence or absence of denuded oocytes (DOs) from the same follicles to determine whether mitogenic and/or steroidogenic responses, to combinations of FSH, insulin-like growth factor 1 (IGF1), and dihydrotestosterone (DHT) were influenced by oocyte-secreted factors (OSFs). To further explore the identity of such factors we performed the same experiments, substituting growth differentiation factor 9 (GDF9), a known OSF, for the DO. OSFs and GDF9 both potently enhanced IGF1-stimulated proliferation, and inhibited FSH-stimulated progesterone secretion. Alone, DHT had little effect on DNA synthesis, but significantly enhanced the mitogenic effects of OSFs or GDF9 in the presence of IGF1. Denuded oocytes, GDF9, and DHT independently inhibited FSH-stimulated progesterone secretion, and androgen, together with DO or GDF9, caused the most potent steroidogenic inhibition. Focusing on mitogenic effects, we demonstrate that both natural androgen receptor (AR) agonists, testosterone and DHT, dose-dependently augmented the mitogenic activity of DO or GDF9. Antiandrogen (hydroxyflutamide) treatment, which is used to block androgen receptor activity, opposed the interaction between androgen and GDF9. In conclusion, androgens stimulate porcine MGC proliferation in vitro by potentiating the growth-promoting effects of oocytes or GDF9, via a mechanism that involves the AR. These signaling pathways are likely to be important regulators of folliculogenesis in vivo, and may contribute to the excess follicle growth that is observed in androgen-treated female animals.

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16471775 PMID: 15998502
Ovarian function in ruminants.
Berisha B; Schams D
Department of Physiology, Technical University Munich-Weihenstephan, Weihenstephaner Berg 3, D-85354 Freising, Germany.
Domestic animal endocrinology (United States) Aug 2005, 29 (2) p305-17, ISSN 0739-7240--Print Journal Code: 8505191
Publishing Model: Print-Electronic
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The purpose of this overview is to highlight important steps of ovarian regulation during follicle development, ovulation and the life span of corpus luteum (CL) in ruminants. The ovarian cycle is central to reproductive function. It is characterized by repeating patterns of cellular proliferation, differentiation and transformation that encompass follicular development and ovulation as well as the formation, function and regression of the CL. In the first part, the importance and regulation of final follicle growth and especially of angiogenesis and blood flow during folliculogenesis, dominant follicle development and CL formation are described. Our results underline the importance of growth factors especially of insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) for development and completion of a dense network of capillaries (angiogenesis) during follicle growth and CL formation. In the second part, the regulation of CL function by endocrine/paracrine and autocrine acting regulators is discussed. There is evidence that besides the main endocrine hormones luteinizing hormone (LH) and growth hormone (GH) local regulators as growth factors, peptides, steroids and prostaglandins are important modulators of luteal function. During early CL development until mid luteal stage oxytocin (OT), prostaglandins and progesterone (P) itself stimulate luteal cell proliferation and function supported by the luteotropic action of a number of growth factors. The still high mRNA expression, protein concentration and localization of VEGF, FGF and IGF family members in the cytoplasm of luteal cells during mid luteal stage suggest that they play pivotal role in the maintenance (survival) of this endocrine tissue. The major function of the CL is to secrete P. Progesterone itself regulates the length of the estrous cycle via influencing the timing of the luteolytic PGF2alpha signal from the endometrium. At the end of a nonfertile cycle, the regression of CL commences, steroidogenic capacity is lost (functional luteolysis), cell death is initiated, and tissue involution as well as resorption occurs within a few days (structural luteolysis). The cascade of mediators during luteolysis is very complex and still awaits elucidation. Evidence is given for participation of blood flow, inflammatory cytokines, vasoactive peptides (angiotensin II and endothelin-1), and decrease of the classical luteotropic mediators.

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16449608 PMID: 15970010
Recombinant LH in ovarian stimulation.
Caglar Gamze Sinem; Asimakopoulos Byron; Nikolettos Nikos; Diedrich Klaus; Al-Hasani Safaa
Department of Obstetrics and Gynecology, Medical University, Lubeck, Germany.
Reproductive biomedicine online (England) Jun 2005, 10 (6) p774-85, ISSN 1472-6483--Print Journal Code: 101122473
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The advent of recombinant gonadotrophins brought significant changes in fertility therapy. Treatment options with recombinant gonadotrophins add more to knowledge on folliculogenesis and ovarian steroidogenesis. Over a decade, recombinant LH (rLH) has been used for clinical trials, and the amount of peripheral LH that is necessary for optimal follicular growth, oocyte maturation, subsequent embryo development and assisted reproduction outcome during ovulation induction can now be better evaluated. This review evaluates the effect of rLH supplementation on ovarian stimulation and assisted reproduction outcome. The studies conducted with rLH supplementation in ovarian stimulation in different groups of patients and in cases of controlled ovarian stimulation are clearly discussed in this review.

15/3,AB/25
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16394094 PMID: 15860501
GnRH agonist versus GnRH antagonist in oocyte donation cycles: a prospective randomized study.
Prapas N; Prapas Y; Panagiotidis Y; Prapa S; Vanderzwalmen P; Schoysman R ; Makedos G
4th Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Greece.
Human reproduction (Oxford, England) (England) Jun 2005, 20 (6) p1516-20, ISSN 0268-1161--Print Journal Code: 8701199
Publishing Model Print-Electronic
Document type: Clinical Trial; Comparative Study; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: The specific role of LH in folliculogenesis and oocyte maturation is unclear. GnRH antagonists, when administered in the late follicular phase, induce a sharp decrease in serum LH which may be detrimental for IVF outcome. This study was performed to evaluate whether the replacement of GnRH agonist (triptorelin) by a GnRH antagonist (ganirelix; NV Organon) in oocyte donation cycles has any impact on pregnancy and implantation rates. METHODS: A total of 148 donor IVF cycles was randomly assigned to use either a GnRH antagonist daily administered from the 8th day of stimulation (group I) or a GnRH agonist long protocol (group II) for the ovarian stimulation of their donors. The primary endpoints were the pregnancy and the implantation rates. RESULTS: The clinical pregnancy rate per transfer (39.72% 29/73 versus 41.33% 31/75) based on transvaginal scan findings at 7 weeks of gestation, the implantation rate (29.9 versus 25.4%) and the first trimester abortion rate (10.34 versus 12.90%) were similar in the two groups. CONCLUSION: In oocyte donation cycles the replacement of GnRH agonist by a GnRH antagonist appears to have no impact on the pregnancy and implantation rates when its administration starts on day 8 of stimulation.

15/3,AB/26
DIALOG(R)File 155:MEDLINE(R)

16343983 PMID: 15836954
Molecular biology and physiological role of the oocyte factor, BMP-15.
Moore R Kelly; Shimasaki Shunichi
Department of Reproductive Medicine, University of California San Diego, School of Medicine, 9500 Gilman Dr., La Jolla, CA 92093-0633, USA.
Molecular and cellular endocrinology (Ireland) Apr 29 2005, 234 (1-2) p67-73, ISSN 0303-7207--Print Journal Code: 7500844
Contract/Grant No.: F32 HD41320; HD; United States NICHD; R01 HD41494; HD ; United States NICHD; U54HD12303; HD; United States NICHD
Publishing Model Print
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The oocyte factor, bone morphogenetic protein-15 (BMP-15) has proven to be critical for normal fertility in female mammals. The biological functions of recombinant BMP-15 demonstrate its capacity to promote granulosa cell processes involved in early follicle growth, while simultaneously acting to restrict follicle-stimulating hormone (FSH)-induced granulosa cell differentiation. The in vitro biological activities of BMP-15 demonstrate its role in promoting early follicle growth through the stimulation of granulosa cell mitosis while simultaneously restricting FSH-induced follicle development through the suppression of FSH receptor mRNA expression. The in vivo relevance of the role of BMP-15 was established by the identification of naturally occurring BMP-15 mutations in sheep, which cause infertility in homozygous carrier ewes and, in striking contrast, increased fecundity in heterozygous carrier ewes due to an increase in ovulation quota. The necessity of BMP-15 for folliculogenesis in women has been recently established by the discovery of a BMP-15 mutation that is associated with ovarian dysgenesis. In contrast to the pronounced effects that the BMP-15 mutations have on folliculogenesis in sheep and humans, mice, which are homozygous for targeted deletions of BMP-15 exhibit only minimal defects in the ovulation process, leading to the proposal that there may be causal differences in the BMP-15 system of mono- and polyovulatory animals. Collectively, recent research on the oocyte-secreted factor BMP-15 has provided exciting new opportunities for understanding ovarian physiology and female fertility.

16340208 PMID: 15834173
[Role of follicular fluid analysis in assessment of the main criteria of folliculogenesis in IVF program]
Tsagareishvili G G
Georgian medical news (Georgia (Republic)) Feb 2005, (119) p18-23, ISSN 1512-0112--Print Journal Code: 101218222
Publishing Model: Print
Document type: Comparative Study; English Abstract; Journal Article
Languages: RUSSIAN
Main Citation Owner: NLM
Record type: MEDLINE; Completed
A comparative study was carried out to assess the main criteria of folliculogenesis in follicular fluid of aspirated follicles during the induction of super ovarian stimulation using recombinant follicle stimulating hormone (r-FSH; Gonal-F), human menopausal gonadotropin (HMG; Pergonal) and agonist gonadotropin releasing hormone (a-GnRH; Diphereline 3,75 mg). 86 patients were included in the study: 37 were receiving r-FSH and 49 HMG, two ampoules per day during the first 5 days of stimulation. Ultrasound monitoring was used for every individual follicle on the first day of stimulation and starting from the 5th day, daily. Thus, the visualized follicles were identified and measured, photoregistered during the whole period of ultrasound guidance. During the transvaginal puncture of these follicles the aspirated follicular fluid volume, existence of oocytes, and its estradiol hormones were recorded. It was found that the follicles in both groups of patients having larger volume of follicular fluid (3 to 5 or >5mm) reached the preovulational size earlier (diameter 17 mm), and on the day of injection of human chorionic gonadotropin (HCG; 10000 IU) had a large size (20 to 21 mm). The positive statistically significant correlation has been observed between the volume of follicular fluid and existence of oocytes in aspirated follicular fluid, as well as with the intensity of their cleavage. The concentration of testosterone and estradiol in follicular fluid was lower in the patients receiving r-FSH (average 12.4 nmol/l, range 9.3-15.1 and 1897113 pmol/l; range 1609216-2185012) than in the patients receiving HCG (16.0 nmol/l; range 12.1-19.6 and 2233728 pmol/l; range 2028660-2438718). The concentration of testosterone in non-pregnant patients receiving r-FSH was 13.7-/+1.0 nmol/l, receiving HMG 16.3-/+0.9 nmol/l, versus 10.3-/+0.8 nmol/l and 14.8-/+0.7 nmol/l, in the patients receiving r-FSH and HMG, respectively, who became pregnant. Thus, the comparative study of main criteria of folliculogenesis in follicular fluid proved to be more preferable and sufficient using FSH in the ovarian stimulation protocol in IVF program.

16280439 PMID: 15758864
Use of GNRH antagonists in reproductive medicine.
Merviel P; Najas S; Carpy H; Floret S; Brasseur F
Department of Obstetrics, Gynecology and Assisted Reproductive Technology, CHU Amiens, Amiens, France. merviel.philippe@chu-amiens.fr
Minerva ginecologica (Italy) Feb 2005, 57 (1) p29-43, ISSN 0026-4784--Print Journal Code: 0400731
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Gonadotrophin-releasing hormone (GnRH) plays a key role in the secretion of gonadotrophins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which regulate steroidogenesis and folliculogenesis. Two GnRH antagonists, Cetrorelix and Ganirelix, deprived of histaminergic side-effects, have been introduced into ovarian stimulation protocols to prevent premature LH surges and proved their safety in clinical trials. At present, most of the published studies have not found significant differences in follicular recruitment, oocyte quality, and so on, except for a decrease in pregnancy and implantation rates in in vitro fertilization and embryo transfer (IVF-ET) cycles when the GnRH antagonist rather than the agonist was used. This decrease in pregnancy rates was in relation with a necessary learning curve of the physicians. Another possibility is the impact of the GnRH antagonist on endometrium through its GnRH receptor; this effect was cancelled after cryopreserved embryo transfers because the pregnancy rates were similar between GnRH antagonist and agonist in this case. GnRH antagonists were also interesting in poor responders and polycystic ovarian syndrome, where the agonists have not permitted to obtain the better results in IVF-ET cycles. Similarly, the GnRH antagonists could prevent the LH surge in the intrauterine insemination cycles.

15/3,AB/29
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16184110 PM ID: 15486232
The orphan nuclear receptors NURR1 and NGFI-B modulate aromatase gene expression in ovarian granulosa cells: a possible mechanism for repression of aromatase expression upon luteinizing hormone surge.
Wu Yimin; Ghosh Sagar; Nishi Yoshihiro; Yanase Toshihiko; Nawata Hajime; Hu Yanfen
Department of Biochemistry and Molecular Genetics, School of Medicine, University of Virginia, Charlottesville, Virginia 22908-0733, USA.
Endocrinology (United States) Jan 2005, 146 (1) p237-46, ISSN 0013-7227--Print Journal Code: 0375040
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, U.S. Gov't, Non-P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Ovarian granulosa cells play pivotal roles in many aspects of ovary functions including folliculogenesis and steroidogenesis. In response to FSH and LH, the elevation of intracellular cAMP level in granulosa cells leads to activation of multiple ovarian genes. Here, we report findings from a genome-wide study of the cAMP-responsive gene expression profiles in a human granulosa-like tumor cell line, KGN. The study identified 140 genes that are either activated or repressed by 2-fold or greater after stimulation by the adenylyl cyclase activator forskolin. The induction patterns of some cAMP-responsive genes were further analyzed by quantitative real-time PCR. Consistent with previous observations, the LH-responsive genes, such as the nuclear receptor 4A subfamily (NURR1, NGFI-B, and NOR-1), were rapidly but transiently induced, whereas the FSH-responsive gene CYP19 encoding aromatase was induced in a delayed fashion. Interestingly, ectopic expression of NURR1 or NGFI-B severely attenuated the cAMP-responsive activation of the ovary-specific aromatase promoter. Reduction of the endogenous NURR1 or NGFI-B by small interfering RNA significantly elevated aromatase gene expression. The cis-elements responsible for NURR1/NGFI-B-mediated repression were mapped to the minimal aromatase promoter sequence that confers camp responsiveness. Furthermore, the DNA-binding domain of NURR1 was required for the repression. Taken together, these results strongly suggest a causal relationship between the rapid decline of aromatase mRNA and induction of nuclear receptor subfamily 4A expression, which concomitantly occur upon LH surge at the later stages of ovarian follicular development.

15/3,AB/30
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15973903 PM ID: 15380756
[Biological effects of GnRH antagonists]
Les antagonistes du GnRH: effets biologiques.
Devaux A; Pouly J-L; Bachelot A; Mbarouvin Z; de Mouzon J
FIVNAT, CHU Bicetre, 82, rue du General-Leclerc, 94276 Le Kremlin-Bicetre, France. avivа.devaux@bch.ap-hop-paris.fr
Gynecologie, obstetrique & fertilite (France) Sep 2004, 32 (9) p741-7, ISSN 1297-9589--Print Journal Code: 100936305
Publishing Model: Print
Document type: English Abstract; Journal Article
Languages: FRENCH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Numerous questions about the efficacy of GnRH antagonists, known for the prevention of undesirable LH surge, have been raised. Although in 2002 in a meta-analysis, IVF Germany Register and FIVNAT the French data base in 2003, have shown a decrease of the pregnancy rate after antagonists treatment. Among 20761 ART attempts for good prognosis women (<35 years, i.v.f. range 1 or 2) we have compared the clinical and biological parameters after agonists' long protocol versus antagonist treatment. The characteristics of the responses to the stimulation treatment were similar for both groups, whereas the duration of the stimulation and the doses of gonadotrophin used in the antagonist group was lower. The fertilization and embryo development rates were not modified. But we observed a decrease in the number of oocytes retrieved, of embryos obtained and of the pregnancy rate (P < 0.001). These results could be explained by endometrial modifications induced by antagonists but we cannot exclude an impact of oestradiol and LH levels. GnRH antagonists could be an inhibitor of the cell cycle by decreasing the synthesis of growth factors. The interaction of GnRH antagonists and GnRH receptors may compromise the mitotic programme of the cells and induce an alteration of folliculogenesis, embryo quality and implantation. More studies are necessary to understand these results. Using of GnRH antagonists involves

specific patient information on the benefits and drawbacks of such treatment before ART.

15/3, AB/31
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15878616 PMID: 15087430
Pregnancy-associated plasma protein-a production in rat granulosa cells: stimulation by follicle-stimulating hormone and inhibition by the oocyte-derived bone morphogenetic protein-15.
Matsui Motozumi; Sonntag Barbara; Hwang Seong Soo; Byerly Tara; Hourvitz Ariel; Adashi Eli Y; Shimasaki Shunichi; Erickson Gregory F
Department of Reproductive Medicine, University of California San Diego, La Jolla, California 92093-0674, USA.
Endocrinology (United States) Aug 2004, 145 (8) p3686-95,
ISSN 0013-7227--Print Journal Code: 0375040
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Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Pregnancy-associated plasma protein-A (PAPP-A) is the major IGF binding protein-4 (IGFBP-4) protease in follicular fluid, consistent with its proposed role in folliculogenesis. Despite growing interest, almost nothing is known about how PAPP-A expression is regulated in any tissue. Here we show that FSH and oocytes regulate PAPP-A expression in granulosa cells (GCs). By in situ hybridization, ovary PAPP-A mRNA was markedly increased by pregnant mare serum gonadotropin treatment, and the message was localized to the membrana GCs but not cumulus GCs (COCs) of dominant follicles. To explore the mechanism we used primary cultures of rat GCs. Control (untreated) cells produced little or no PAPP-A spontaneously. Conversely, FSH markedly stimulated PAPP-A mRNA and protein in a dose- and time-dependent fashion. Interestingly, PAPP-A expression in isolated COCs was also strongly induced by FSH, and the induction was inhibited by added oocytes. To investigate the nature of the inhibition, we tested the effect of oocyte-derived bone morphogenetic protein-15 (BMP-15). BMP-15 alone had no effect on basal levels of PAPP-A expression by cultures of membrana GCs or COCs. However, BMP-15 markedly inhibited the FSH stimulation of PAPP-A production in a dose-dependent manner. The cleavage of IGFBP-4 by conditioned media from FSH-treated GCs was completely inhibited by anti-PAPP-A antibody, indicating the IGFBP-4 protease secreted by GCs is PAPP-A. These results demonstrate stimulatory and inhibitory roles for FSH and BMP-15, respectively, in regulating PAPP-A production by GCs. We propose that FSH and oocyte-derived BMP-15 form a controlling network that ensures the spatiotemporal pattern of GC PAPP-A expression in the dominant follicle.

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15672671 PMID: 15019464
Influences of FSH and EGF on primordial follicles during in vitro culture of caprine ovarian cortical tissue.
Silva Jose R V; van den Hurk Rob; de Matos Maria H T; dos Santos Regiane R; Pessoa Claudia; de Moraes Manoel O; de Figueiredo Jose R
Faculty of Veterinary Medicine, PPGCV, State University of Ceara, Fortaleza, CE, Brazil. j.r.v.silva@vet.uu.nl
Theriogenology (United States) Jun 2004, 61 (9) p1691-704,
ISSN 0093-691X--Print Journal Code: 0421510
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Factors that control the onset of folliculogenesis are critical to female gamete production, but poorly understood. The aim of the present study was to investigate the effects of FSH and EGF on the activation and growth of goat primordial follicles in vitro. To this end, pieces of goat ovarian cortex were cultured in vitro for 1, 3 or 5 days, at 39 degrees C in an atmosphere containing 5% CO(2), in minimum essential medium supplemented with insulin, transferrin, selenium, pyruvate, glutamine, hypoxanthine, BSA, penicillin, streptomycin and fungizone and with or without FSH (100 ng/ml) and/or EGF (100 ng/ml). At the end of the culture periods, the relative proportions of primordial, intermediate, primary and secondary follicles were calculated and compared with those in non-cultured tissue. In addition, mitotic activity of granulosa cells was studied by immunohistochemistry for proliferating cell nuclear antigen (PCNA). In brief, it was found that goat primordial follicles activate spontaneously during culture in vitro and, while neither FSH nor EGF

affected the proportion of primordial follicles that entered the growth phase, both stimulated an increase in oocyte and follicle diameter, especially in intermediate and primary follicles cultured for 5 days. On the other hand, there was no significant effect of culture or either growth factor on the proportion of PCNA-stained growing follicles. Contrary to expectations, neither FSH nor EGF affected follicle viability or integrity during culture, since the percentages of intact follicles did not differ between control, FSH and/or EGF containing medium. In conclusion, this study demonstrated that goat primordial follicles activate spontaneously in vitro, and that both FSH and EGF stimulate an increase in follicle size by promoting oocyte growth.

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15539313 PMID: 14748688
Ovarian gonadotrophin surge-attenuating factor (GnSAF): where are we after 20 years of research?
Fowler Paul A; Sorsa-Leslie Tarja; Harris William; Mason Helen D
Department of Obstetrics and Gynaecology, University of Aberdeen, Aberdeen AB25 2ZD, UK. p.a.fowler@abdn.ac.uk
Reproduction (Cambridge, England) (England) Dec 2003, 126 (6) p689-99, ISSN 1470-1626--Print Journal Code: 100966036
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
When gonadotrophin-stimulated IVF methods were being developed in the 1970s and 1980s, understanding of the physiology of FSH improved. In addition to its classic actions of stimulating aromatase activity and oestradiol secretion by ovarian granulosa cells, FSH was found to stimulate the ovarian production of an uncharacterized hormone known by its specific effect of reducing pituitary responsiveness to GnRH. This hormone has been called gonadotrophin surge-attenuating factor (GnSAF), gonadotropin surge-inhibiting factor (GnSIF), various abbreviations (GnSAF/IF, GnSIF/AF) and also attenuin. Although first described in the 1980s, GnSAF has still not been convincingly characterized and no published candidate amino acid sequences conclusively relate to GnSAF bioactivity. On the basis of superovulation studies and in vitro experimentation into the roles of steroids in regulating LH, GnRH and GnRH self-priming, the concept that GnSAF has a role in the regulation of LH secretion, the timing of the LH surge and the prevention of premature luteinization developed. For at least a decade, understanding of the specific GnSAF effects of reducing pituitary sensitivity to GnRH, especially GnRH self-priming and antagonizing the stimulatory effects of oestradiol on GnRH-induced LH secretion, supported this concept. However, improved knowledge of the changes in GnSAF bioactivity in follicular fluid and serum in women requires revision of this concept. The present authors propose that the main role of GnSAF is probably the negative regulation of pulsatile LH secretion, mainly during the first half of the follicular phase, indicating a critical role in the regulation of folliculogenesis and oestradiol secretion.

15/3,AB/34
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15478467 PMID: 14635928
Mechanisms regulating follicular development and selection of the dominant follicle.
Webb R; Nicholas B; Gong J G; Campbell B K; Gutierrez C G; Garverick H A; Armstrong D G
Division of Agricultural Sciences, School of Biosciences, University of Nottingham, Loughborough LE12 5RD, UK. bob.webb@nottingham.ac.uk
Reproduction (Cambridge, England) Supplement (England) 2003, 61 p71-90, ISSN 1477-0415--Print Journal Code: 101142074
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Reproductive function is an integrated process encompassing both extra-ovarian signals, such as gonadotrophins, and intrafollicular factors, such as locally produced growth factors. Initiation of primordial follicle growth and the early stages of folliculogenesis can occur without gonadotrophins. However, in vivo and in vitro studies indicate that FSH may stimulate the rate of preantral follicle growth and that it can take only 3 months for a primordial follicle to reach the ovulatory stage. Antral follicle development from 2 and 4 mm in diameter in sheep and cattle, respectively, is gonadotrophin dependent. During the oestrous cycle a transient increase in circulating FSH precedes the

recruitment of a group of follicles. Recruited follicles are characterized by induction of expression of mRNAs encoding a range of steroidogenic enzymes, gonadotrophin receptors and local regulatory factors. As follicles continue to mature, there is a transfer of dependency from FSH to LH, which may be part of the mechanism involved in selection of follicles for continued growth. The mechanism of selection of the ovulatory follicle seems to be linked to the timing of mRNA expression encoding LHr and 3beta-hydroxysteroid dehydrogenase (3beta-HSD) in granulosa cells. Locally produced growth factors, such as the insulin-like growth factors (IGFs) and members of the transforming growth factor beta (TGFbeta) superfamily (inhibins, activins and bone morphogenetic proteins (BMPs)), work in concert with gonadotrophins throughout the follicular growth continuum. The roles of growth factors in follicular development and survival are dependent on gonadotrophin status and differentiation state, including morphology. In conclusion, it is the integration of extraovarian signals and intrafollicular factors that determine whether a follicle will continue to develop or be diverted into atretic pathways, as is the case for most of the follicles in monovulatory species, such as cattle.

15/3,AB/35
DIALOG(R)File 155:MEDLINE(R)
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15453857 PMID: 14607566
A double-blind, randomized, placebo-controlled study to assess the efficacy of ketoconazole for reducing the risk of ovarian hyperstimulation syndrome.
Parsanezhad Mohammad Ebrahim; Alborzi Saeed; Pakniat Mahnaz; Schmidt Ernst Heinrich
Shiraz University of Medical Sciences, Shiraz, Iran. parsame@sums.ac.ir
Fertility and sterility (United States) Nov 2003, 80 (5) p1151-5, ISSN 1015-0282--Print Journal Code: 0372772
Publishing Model: Print
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: To evaluate the role of ketoconazole in prevention of ovarian hyperstimulation syndrome (OHSS) in women with the polycystic ovary syndrome (PCOS) undergoing ovarian stimulation with gonadotropins.
DESIGN: Prospective, randomized, double-blind, placebo-controlled study.
SETTING: University hospitals.One hundred nine women with PCOS who were referred for treatment with gonadotropins.
INTERVENTION(S): Fifty patients were randomly assigned to receive two ampoules of hMG beginning on day 2 or 3 of the cycle and ketoconazole (50 mg every 48 hours) starting on the first day of hMG treatment. Fifty-one patients received the same amount of hMG plus one tablet of placebo every 48 hours.
MAIN OUTCOME MEASURE(S): Follicular development, E(2) level, and pregnancy rate.
RESULT(S): The total number of hMG ampoules and duration of treatment to attain ovarian stimulation were higher among ketoconazole recipients. The serum E(2) level and number of patients with dominant follicles on day 9 of the cycle were greater in placebo recipients. Serum E(2) level and total number of follicles at the time of hCG administration did not differ between the two groups. The cancellation rate and OHSS rate were similar in the two groups.
CONCLUSION(S): Ketoconazole does not prevent OHSS in patients with PCOS who are undergoing ovarian stimulation. It may reduce the rate of folliculogenesis and steroidogenesis.

15/3,AB/36
DIALOG(R)File 155:MEDLINE(R)
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15450506 PMID: 14604074
Dynamic evaluation of ovarian reserve and abnormal androgen excess in women.
Moretti C; Toscano V
Department of Internal Medicine, Unit of Endocrinology, University of Rome Tor Vergata, Fatebenefratelli Hospital Isola Tiberina, Rome, Italy.
Journal of endocrinological investigation (Italy) 2003, 26 (7 Suppl) p114-23, ISSN 0391-4097--Print Journal Code: 7806594
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The evaluation of the ovarian reserve is an important area of clinical investigation that gives information on endowment and functional activity of remaining follicles within the ovary, thus concerning the female reproductive potential. In neonatal and pediatric age, an ovarian failure is commonly due to disorders of sexual differentiation. In adults, the basal and dynamic tests that predict the ovarian reserve are particularly useful in women undergoing assisted reproductive programs. Transvaginal

ultrasound study of ovarian folliculogenesis performed simultaneously with the evaluation of cervical score, FSH, LH and estradiol plasma levels, evidentiates follicular rupture and ovulation, indicating also the optimum timing of hCG administration. Basal day 3 FSH, 17-beta-estradiol and inhibin B plasma levels give information on the ovarian potential. Clomiphene citrate challenge test (CCCT) and GnRH agonist stimulation test (GAST) have clinical utility as indicators of ovarian reserve but their accuracy does not allow to be predictive in terms of number-per-unit tissue of the remaining follicle within the ovary. In the present paper the strategies to study hyperandrogenism and polycystic ovarian syndrome, a common cause of ovarian reserve reduction and subfertility, are also reviewed. The abnormal androgen excess in women can be referred to the ovary, the adrenal glands, or the peripheral conversion of androgen precursors. Dynamic tests may be useful for determining the amount of androgens rising from each of these sites helping the therapeutic strategies.

15/3,AB/37
DIALOG(R)File 155:MEDLINE(R)
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15434320 PMID: 14580642
Effects of hCG on folliculogenesis and fecundity in mink (Mustela vision Schreb).
Klotchkov D V; Eryuchenkov P A
Laboratory of Evolutionary Genetics, Institute of Cytology and Genetics, Siberian Department Russian Academy of Sciences, Novosibirsk 630090, Russia. iplysn@sinet.nsc.ru
Theriogenology (United States) Dec 2003, 60 (9) p1583-93, ISSN 0093-691X--Print Journal Code: 0421510
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The endogenous hormonal response obtained after reproductive organs are challenged by exogenous hormones is increasingly being used to predict presence of functional reserves and to apply this information to improve efficiency of managed breeding programs. With that in mind, the aim of the present study was to investigate the effect of a single treatment with hCG on folliculogenesis and fertility in standard 7-month-old mink females. The extent of stimulation following treatment was determined by examining patterns of vaginal smears. Characteristics of each cycle stage were: estrus, preponderance of cornified epithelial cells; proestrus, polygonal, elongate epithelial cells; anestrus, parabasal, intermediate and leucocyte cells. Smears exhibiting a mixed population of cells were categorized as being in transition between adjacent stages anestrus-proestrus or proestrus-estrus. The initial evaluations were done on Day 6 after hCG treatment. Histomorphometric examination of ovaries and uteri was done during seasonal anestrus (November) and in the breeding season (March). Vaginal cytology patterns were correlated with changes in folliculogenesis. A mean of 1.3 mature (Graafian) follicles were counted during estrus, while the mean number seen during anestrus, anestrus-proestrus and proestrus, were 0.4, 0.3 and 1.0, respectively. During the breeding season, in females that were not treated, the numbers of growing follicles decreased and maturing follicles increased, whereas females that came in estrus after treatment with hCG in November had increased numbers of both growing and maturing follicles. Fertility after breeding in hCG-treated females was increased by 9.2% (P<0.05) as compared to untreated females. Females showing the highest fertility rise (27%) were predominantly in the group that showed estrus after hCG treatment. We conclude that monitoring the response of the mink reproductive system to hCG stimulation in November may be a useful tool for identifying females of high fertility in the spring.

15/3,AB/38
DIALOG(R)File 155:MEDLINE(R)
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15422196 PMID: 12890736
Expression and functional role of peroxisome proliferator-activated receptor-gamma in ovarian folliculogenesis in the sheep.
Froment Pascal; Fabre Stephane; Dupont Joelle; Pisselet Claudine; Chesneau Didier; Staels Bart; Monget Philippe
Physiologie de la Reproduction et des Comportements, UMR 6073 INRA-CNRS-Universite F. Rabelais de Tours, 37380 Nouzilly, France.
Biology of reproduction (United States) Nov 2003, 69 (5) p1665-74, ISSN 0006-3363--Print Journal Code: 0207224
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM

Record type: MEDLINE; Completed

Peroxisome proliferator-activated receptor (PPARgamma) is a nuclear receptor that is activated by fatty acids and derivatives and the antidiabetic glitazones, which plays a role in the control of lipid and glucose homeostasis. In the present work, we tested the hypothesis that PPARgamma plays a role in reproductive tissues by studying its expression and function in the hypothalamo-pituitary-ovary axis in the sheep. PPARgamma 1 and PPARgamma 2 proteins and mRNAs were detected in whole ovine pituitary and ovary but not in hypothalamic extracts. In situ hybridization on ovarian section localized PPARgamma mRNA in the granulosa layer of follicles. Interestingly, PPARgamma expression was higher in small antral (1-3 mm diameter than in preovulatory follicles (>5 mm diameter) (P < 0.001) and was not correlated with healthy status. To assess the biological activity of ovarian PPARgamma, ovine granulosa cells were transfected with a reporter construct driven by PPARgamma-responsive elements. Addition of rosiglitazone, a PPARgamma ligand, stimulated reporter gene expression, showing that endogenous PPARgamma is functional in ovine granulosa cells in vitro. Moreover, rosiglitazone inhibited granulosa cell proliferation (P < 0.05) and increased the secretion of progesterone in vitro (P < 0.05). This stimulation effect was stronger in granulosa cells from small than from large follicles. In contrast, rosiglitazone had no effect on LH, FSH, prolactin and growth hormone secretion by ovine pituitary cells in vitro. Overall, these data suggest that PPARgamma ligands might stimulate follicular differentiation in vivo likely through a direct action on granulosa cells rather than by modulating pituitary hormone secretion.

15/3,AB/39
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15316333 PMID: 12909504

Comparison of controlled ovarian stimulation with human menopausal gonadotropin or recombinant follicle-stimulating hormone.

Filicori Marco; Cognigni Graciela E; Pocognoli Patrizia; Tabarelli Cristina; Ferlini Federica; Pedori Tiziana; Parmegiani Lodovico

Reproductive Endocrinology Center, University of Bologna, Bologna, Italy. marco.filicori@unibo.it

Fertility and sterility (United States) Aug 2003, 80 (2) p390-7, ISSN 0015-0282--Print Journal Code: 0372772

Publishing Model Print

Document type: Clinical Trial; Comparative Study; Journal Article; Randomized Controlled Trial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

OBJECTIVE: To carefully examine the features of controlled ovarian stimulation performed with recombinant FSH-alpha or hMG. DESIGN: Controlled, prospective, randomized comparison of fixed gonadotropin regimens. SETTING: Academic research institution. PATIENT(S): Fifty infertile patients who were candidates for IUI. INTERVENTION(S): Patients were randomized to receive a fixed regimen of recombinant FSH-alpha (150 IU/day, 25 patients) or hMG (150 IU/day, 25 patients) after GnRH-agonist suppression (long regimen). MAIN OUTCOME MEASURES: Daily measurements of serum LH, immunoreactive FSH, hCG, E(2), P, and T. Transvaginal pelvic ultrasound every 2 days. Pregnancy and abortion rates. Cost of medications. Two recombinant FSH-alpha-treated patients did not respond. Despite matched daily FSH dose, duration of treatment (hMG 10.8 +/- 0.4 vs. recombinant FSH-alpha 12.4 +/- 0.5 days), gonadotropin dose (21.7 +/- 0.8 vs. 25.3 +/- 1.3 ampoules), gonadotropin cost (288 +/- 10 vs. 1,299 +/- 66 /cycle), serum P levels, and small preovulatory follicle number were significantly lower, and LH, hCG, immunoreactive FSH levels, and larger follicles on day 8 were significantly higher in hMG-treated patients. The pregnancy, abortion, and twin pregnancy rates did not differ. CONCLUSION: The hMG administration was associated with: [1]. increased serum LH activity and immunoreactive FSH levels during treatment; [2]. reduced signs of premature luteinization; [3]. differential modulation of folliculogenesis; [4]. lower treatment duration, gonadotropin dose, and cost; and [5]. clinical outcome comparable to recombinant FSH-alpha.

15/3,AB/40
DIALOG(R)File 155:MEDLINE(R)
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15302582 PMID: 12890591

Current concepts and novel applications of LH activity in ovarian stimulation.

Filicori Marco; Cognigni GracielaE; Pocognoli Patrizia; Ciampaglia Walter; Bernardi Silvia

Reproductive Endocrinology Center, University of Bologna, Via Massarenti 13, 40138 Bologna, Italy. marco.filicori@unibo.it

Trends in endocrinology and metabolism: TEM (United States) Aug 2003; 14 (6) p267-73; ISSN 1043-2760--Print Journal Code: 9001516
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Luteinizing hormone (LH) is a crucial physiological regulator of the human menstrual cycle. LH activity is also contained in many medications used to treat anovulation and to stimulate multiple folliculogenesis for assisted reproduction techniques. However, LH activity had previously been regarded as just a contaminant of follicle-stimulating hormone (FSH)-containing products and deemed potentially detrimental for reproductive function. Novel experimental and clinical evidence now suggests that the administration of pharmacological amounts of LH activity, instead of being harmful, is therapeutically advantageous, particularly in the support and modulation of ovarian folliculogenesis. The aim of this article is to provide an overview of the effects of LH activity administration in ovarian stimulation and to outline novel unconventional gonadotropin regimens that might improve the efficacy, safety and convenience of ovulation induction.

15/3,AB/41
DIALOG(R)File 155:MEDLINE(R)
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15253847 PMID: 12831587
Pregnancy after administration of high dose recombinant human LH alone to support final stages of follicular maturation in a woman with long-standing hypogonadotrophic hypogonadism.
Balasch Juan; Fabregues Francisco
Institut Clinic of Gynecology, Obstetrics and Neonatology, Faculty of Medicine-University of Barcelona, Hospital Clinic-Institut d'Investigacions Biomediques August Pi i Sunyer, Barcelona, Spain. jbalasch@medicina.ub.es
Reproductive biomedicine online (England) Jun 2003; 6 (4) p427-31; ISSN 1472-6483--Print Journal Code: 101122473
Publishing Model: Print; Comment in Reprod Biomed Online. 2003 Sep;7(2) 254-5; author reply 255-7; Comment in PMID 14567902
Document type: Case Reports; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Traditionally, the roles of LH in folliculogenesis have been considered to be limited to stimulating theca cells androgen production, triggering ovulation and supporting the corpus luteum. However, in the late stages of follicle development, granulosa cells become receptive to LH stimulation and LH becomes capable of exerting its actions on both theca cells and granulosa cells. Thus, it has been postulated that once an appropriate (i.e. LH-responsive) stage of follicular development has been achieved in response to treatment with FSH, there are theoretical grounds for reducing or completely withdrawing FSH and maintaining tonic stimulation of the dominant follicle with exogenous LH. This hypothesis was tested in a woman with long-standing hypogonadotrophic hypogonadism, which is the best and only true model to investigate correctly any LH hypothesis. Ovulation induction treatment was carried out with daily s.c. injections of 150 IU recombinant human FSH (rhFSH) (increased to 225 IU daily on stimulation day 15) and 375 IU recombinant human LH (rhLH). When a 14-mm follicle was identified on stimulation day 26, rhFSH was discontinued and, from treatment days 26 to 29, the patient was given only rhLH at the above-mentioned dose of 375 IU/day. On treatment day 30, the single dominant follicle measured 22 mm in diameter and oestradiol serum concentration was 148 pg/ml. Thus, an injection of 10,000 IU i.m. human chorionic gonadotrophin was given and sexual intercourse was advised. The patient conceived and a viable singleton intrauterine pregnancy was obtained.

15/3,AB/42
DIALOG(R)File 155:MEDLINE(R)
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15177093 PMID: 12740151
Comparison of recombinant human luteinising hormone (r-hLH) and human menopausal gonadotropin (hMG) in assisted reproductive technology.
Baer G; Loumaye E
Laboratoires Serono, Vevey, Switzerland. gianni.baer@serono.com
Current medical research and opinion (England) 2003; 19 (2) p83-8; ISSN 0300-7995--Print Journal Code: 0351014
Publishing Model: Print
Document type: Comparative Study; Journal Article; Review
Languages: ENGLISH

Main Citation Owner: NLM
Record type: MEDLINE; Completed
Follicle-stimulating hormone (FSH) and luteinising hormone (LH) act in concert in the stimulation of folliculogenesis and ovulation. However, high levels of LH promote follicular atresia and early miscarriage, and this has led to the concept of a 'therapeutic window' of LH for successful conception in assisted reproductive technology (ART) and ovulation induction. Until now, urinary-derived human menopausal gonadotropin (hMG) has been the only available source of exogenous LH activity. hMG preparations contain highly variable levels of LH, and are often augmented with human chorionic gonadotropin (hCG), which mimics LH activity. Accumulation of hCG bioactivity, however, may have detrimental effects on follicular development and oocyte quality. Recombinant human LH (r-hLH) (Luveris) is the only pure source of LH activity. r-hLH is well characterised and production is tightly controlled, resulting in a highly consistent product. Clinical studies in hypogonadotropic hypogonadal women have demonstrated the efficacy of r-hLH, 75 IU/day, together with r-hFSH, 150 IU/day, in promoting optimal follicular development, oestrogen secretion and endometrial thickness. r-hLH therefore provides the clinician with the opportunity for precise and consistent dosing within the therapeutic window for patients requiring exogenous LH, without the risk of LH overexposure that is associated with hCG.

15/3,AB/43
DIALOG(R)File 155:MEDLINE(R)
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14999385 PMID: 14666146
Role of LH in controlled ovarian stimulation.
Wiesak Teresa
Shore Institute for Reproductive Medicine, Brick, NJ 08724, USA. twiesak@aol.com
Reproductive biology (Poland) Nov 2002, 2 (3) p215-27, ISSN 1642-431X--Print Journal Code: 101160559
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Controlled ovarian stimulation has become an integral part of infertility treatment. Specific gonadotropin based protocols become the main strategies for controlled stimulation. To avoid the potentially detrimental effect of premature LH surge on oocytes and/or endometrium development, the GnRH analogs have been incorporated into controlled ovarian stimulation strategies. With the availability of recombinant gonadotropins (i.e. recombinant FSH devoided of LH activity) it is necessary to establish precise role of LH in the folliculogenesis and endometrium development. The benefit of exogenous LH may vary with the GnRH-agonists and antagonists regiment used. The optimal amount of LH or ratio FSH to LH used during therapeutically stimulated growth of follicles is still a problem that needs to be solved in the near future.

15/3,AB/44
DIALOG(R)File 155:MEDLINE(R)
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14941289 PMID: 12498424
The use of LH activity to drive folliculogenesis: exploring uncharted territories in ovulation induction.
Filicori Marco; Cognigni Graciela E; Samara Arafat; Melappioni Silvia; Perri Tiziana; Cantelli Barbara; Parmegiani Lodovico; Pelusi Giuseppe; De Aloysio Domenico
Reproductive Endocrinology Center, University of Bologna, Bologna, Italy. filicori@med.unibo.it
Human reproduction update (England) Nov-Dec 2002, 8 (6) p543-57, ISSN 1355-4786--Print Journal Code: 9507614
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
LH plays critical roles in the control of folliculogenesis and ovarian function in humans. LH activity administration during gonadotrophin ovulation induction can enhance ovarian response and optimise treatment. More specifically, LH activity (both LH and low-dose hCG) can support the growth and stimulate the maturation of larger ovarian follicles as a result of specific granulosa cell receptors that develop after a few days of FSH priming. This action of LH is independent of FSH and it has been shown recently that the last stages of follicular development can be supported by sole administration of LH activity in the form of low-dose hCG, without causing

premature luteinization. Reproductively competent oocytes and pregnancy can be obtained with this regimen. Furthermore, LH activity is capable of reducing the development of small ovarian follicles (<10 mm) that may predispose patients to developing complications such as the ovarian hyperstimulation syndrome. Thus, better understanding of the dynamics and mechanisms that control human folliculogenesis and a more rational and selective use of LH activity administration may allow a reduction in cost and increased safety, while maintaining a high efficacy of the ovulation induction regimens used in assisted reproduction.

15/3,AB/45
DIALOG(R)File 155:MEDLINE(R)
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14875045 PMID: 12417011
Folliculogenesis and ovarian expression of mRNA encoding aromatase in anoestrous sheep after 5 days of glucose or glucosamine infusion or supplementary lupin feeding.
Munoz-Gutierrez M; Blache D; Martin G B; Scaramuzzi R J
Department of Veterinary Basic Sciences, Royal Veterinary College, University of London, Royal College Street, UK. rmunoz@vc.ac.uk
Reproduction (Cambridge, England) (England) Nov 2002, 124 (5) p721-31, ISSN 1470-1626--Print Journal Code: 100966036
Publishing Model: Print
Document type: Comparative Study; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Improved nutrition increases ovulation rate in sheep and there is evidence that intra-ovarian pathways mediate responses to nutrition. An experiment was conducted to examine the effect of dietary energy on folliculogenesis. Anoestrous Merino ewes were fed a diet of wheat straw alone (control, n = 5), or wheat straw supplemented with lupins (500 g day(-1), n = 5). Other ewes were fed wheat straw and infused with glucose (50 mmol h(-1), n = 5) or with glucosamine (3.5 mmol h(-1), n = 5). Intravaginal progestagen sponges were inserted for 12 days, and nutritional treatments were started 5 days before sponge removal. At sponge removal, the ewes were injected with a regimen of GnRH pulses (500 ng every 4 h from 0 to 12 h; 250 ng every 2 h from 14 to 24 h; and 200 ng every 1 h from 25 to 36 h) to simulate normal follicular development. Thirty-six hours after sponge removal, the animals were killed and the ovaries were collected and stored at -80 degrees C. The ovaries were sectioned serially every 10 microm. Every 20th section was stained (to estimate number and diameter of follicles) and every 17-19th section was probed by in situ hybridization for P(450) aromatase. Data were analysed using ANOVA and chi-squared tests. There was an effect of treatment ($P < 0.05$) on the number of follicles 2-3, 3-4 and 6-7 mm in diameter. Aromatase-positive follicles (1.6-7.9 mm) were detected in 31 follicles from 15 ewes across all four groups. In ten animals, the largest follicle was aromatase-positive. The diameters of aromatase-positive follicles were larger ($P = 0.004$) in lupin fed compared with glucose-infused ewes (4.9 +/- 0.5, 3.6 +/- 0.7, 5.3 +/- 0.5 and 4.2 +/- 0.5 mm for control, glucose-infused, lupin-fed and glucosamine-infused groups, respectively). Treatment did not affect the plasma concentration of FSH when compared with controls, indicating that the energy supplements were modifying recruited (2-3 mm and 3-4 mm) and selected follicles (> 6 mm) directly. In conclusion, dietary energy can directly stimulate folliculogenesis in recruited and selected follicles; and this effect may be mediated by changes in systemic leptin concentrations and the hexosamine energy-sensing pathway in the follicle.

15/3,AB/46
DIALOG(R)File 155:MEDLINE(R)
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14874476 PMID: 12417300
Identification and functional analysis of novel phosphorylation sites in Cx43 in rat primary granulosa cells.
Yogo Keiichiro; Ogawa Takuya; Akiyama Motofusa; Ishida Norihiro; Takeya Tatsuo
Graduate School of Biological Sciences, Nara Institute of Science and Technology, Ikoma, Nara 630-0101, Japan.
FEBS letters (Netherlands) Nov 6 2002, 531 (2) p132-6, ISSN 0014-5793--Print Journal Code: 0155157
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The gap junctional intercellular communication mediated by Cx43 plays indispensable roles in both germ line development and postnatal folliculogenesis. In this study, we focused on the effect of follicle-stimulating hormone (FSH) on the Cx43 protein in rat primary

granulosa cells and found that FSH stimulation elevated the phosphorylation in addition to the protein level of Cx43. Serine residues in the carboxyl-terminal region were exclusively phosphorylated in this system and we identified Ser365, Ser368, Ser369 and Ser373 as major phosphorylation sites by FSH stimulation. A Cx43 variant containing mutations at all these serine residues was found to severely reduce dye transfer activity when assayed in HeLa cells. The present study revealed a novel regulatory mechanism of Cx43-mediated gap junctional intercellular communication through phosphorylation in the carboxyl-terminus.

15/3,AB/47
DIALOG(R)File 155:MEDLINE(R)
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14736529 PMID: 12151429
Modulation of folliculogenesis and steroidogenesis in women by graded menotrophin administration.
Filicori M; Cognigni G E; Pocognoli P; Tabarelli C; Spettoli D; Taraborrelli S; Ciampaglia W
Reproductive Endocrinology Centre, University of Bologna, Bologna, Italy. filicori@med.unibo.it
Human reproduction (Oxford, England) (England) Aug 2002, 17 (8) p2009-15, ISSN 0268-1161--Print Journal Code: 8701199
Publishing Model Print
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: To test the effects of progressively decreasing dosages of exogenous LH we combined various amounts of HMG containing FSH, LH and hCG, and highly purified (HP) FSH to treat 120 GnRH agonist-suppressed infertile female patients as candidates for controlled ovarian stimulation (COS). METHODS: Subjects were randomly assigned to four treatment groups that received the following daily i.m gonadotrophin regimens: A, FSH 150 IU only; B, FSH 150 IU and LH activity 37.5 IU; C, FSH 150 IU and LH activity 75 IU; D, FSH 150 IU and LH activity 150 IU. FSH dose adjustments were allowed only after the 14th treatment day. Monitoring included transvaginal ultrasound at 2-day intervals and daily determinations of LH, FSH, estradiol (E(2)), progesterone, testosterone and hCG. RESULTS: Duration of COS was significantly shortened in patients receiving at least 75 IU daily of LH activity. Small (<10 mm diameter) pre-ovulatory ovarian follicle occurrence was inversely correlated with LH activity dose administered ($r = -0.648$, $P < 0.0001$) and serum hCG levels ($r = -0.272$, $P < 0.01$) but not to serum LH levels. Serum testosterone levels were positively correlated to the LH activity dose administered ($r = 0.313$, $P < 0.001$), while serum progesterone levels were positively correlated to the FSH dose administered ($r = 0.447$, $P < 0.00001$) but not to the LH activity dose administered. CONCLUSIONS: Firstly, hCG content considerably contributes to HMG activity; secondly, menotrophin LH activity content can reduce in a dose-dependent manner the occurrence of small pre-ovulatory follicles; and finally, contrary to common belief, enhanced FSH stimulation rather than LH activity appears to cause premature follicle luteinization during COS.

15/3,AB/48
DIALOG(R)File 155:MEDLINE(R)
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14724935 PMID: 12137883
Intracytoplasmic sperm injection pregnancy after low-dose human chorionic gonadotropin alone to support ovarian folliculogenesis.
Filicori Marco; Cognigni Graciela Estela; Taraborrelli Stefania; Parmegiani Lodovico; Bernardi Silvia; Ciampaglia Walter
Reproductive Endocrinology Center, Department of Obstetrics and Gynecology, University of Bologna, Bologna, Italy. filicori@med.unibo.it
Fertility and sterility (United States) Aug 2002, 78 (2) p414-6, ISSN 0015-0282--Print Journal Code: 0372772
Publishing Model Print
Document type: Case Reports; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: To prove that several days of low-dose hCG alone can be used to stimulate folliculogenesis, complete FSH-initiated follicle/oocyte maturation, and achieve pregnancy in assisted reproduction technology. DESIGN: Case report. SETTING: Reproductive endocrinology center at an academic institution. PATIENT(S): A 35-year-old female patient and her partner with male-related infertility. INTERVENTION(S): After an 8-day priming with hMG (225 IU/d), we

administered low-dose hCG (200 IU/d) alone for 5 days in one GnRH-agonist suppressed patient until proper follicle development was obtained and intracytoplasmic sperm injection was performed. MAIN OUTCOME MEASURE(S): Daily serum levels of LH, FSH, hCG, E(2), P, and T; measurements of follicle number and size; oocytes retrieved and fertilized; pregnancy. RESULT(S): Although FSH levels rapidly declined after hMG discontinuation, E(2) and large follicles increased during hCG-only administration. Several good quality oocytes were retrieved and fertilized by intracytoplasmic sperm injection; three embryos were transferred and a twin pregnancy ensued. CONCLUSION(S): Replacement of FSH with low-dose hCG for several days in the late ovulation induction stages of assisted reproduction technology resulted in: [1] continued growth of large ovarian follicles and E(2); [2] an optimal preovulatory follicle pattern consisting of many large and few medium and small follicles; and [3] reproductively competent oocytes and pregnancy.

15/3,AB/49
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14724915 PMID: 12137863
A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women.
Fisher Stephanie A; Reid Robert L; Van Vugt Dean A; Casper Robert F
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Queen's University, Kingston General Hospital, Ontario, Canada.
Fertility and sterility (United States) Aug 2002, 78 (2) p280-5, ISSN 0015-0282--Print Journal Code: 0372772
Publishing Model: Print
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: To evaluate the ovarian follicular dynamics of cycle modification with the aromatase inhibitor letrozole compared with clomiphene citrate in normal ovulatory women. DESIGN: Randomized double-blind controlled trial. SETTING: Tertiary care hospital. PATIENT(S): Nineteen ovulatory female volunteers, ages 18-35 years. INTERVENTION(S): Subjects were monitored in one control cycle. Subjects then received either letrozole 2.5 mg daily or clomiphene citrate 50 mg daily on days 5-9 after menses. MAIN OUTCOME MEASURE(S): Number of mature follicles, endometrial thickness and endometrial pattern at ovulation, and follicular profiles of LH, FSH, and E(2). RESULT(S): The number of mature follicles at the LH surge in natural cycles was 1.0 with an exaggerated response seen for treatment both with clomiphene and letrozole. There was no difference in the endometrial thickness at midcycle during either the natural cycles or the medicated cycles. LH surges and spontaneous ovulation were documented in all natural and medicated cycles. When measured daily, follicular profiles of LH and FSH are similar between the groups in both the natural and medicated cycles. In the medicated cycles, clomiphene results in a significant increase in E(2) levels, while E(2) levels in letrozole-stimulated cycles appeared lower than in natural cycles. CONCLUSION(S): Transient inhibition of aromatase activity in the early follicular phase with the aromatase inhibitor letrozole results in stimulation of ovarian folliculogenesis similar to that seen with clomiphene citrate with no apparent adverse effect on endometrial thickness or pattern at midcycle.

15/3,AB/50
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14534997 PMID: 11889180
Stimulation and growth of antral ovarian follicles by selective LH activity administration in women.
Filicori M Cognigni G E; Tabarelli C; Pocognoli P; Taraborrelli S; Spettoli D; Ciampaglia W
Reproductive Endocrinology Center, University of Bologna, Bologna 40138, Italy. filicori@med.unibo.it
Journal of clinical endocrinology and metabolism (United States) Mar 2002, 87 (3) p1156-61, ISSN 0021-972X--Print Journal Code: 0375362
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Intensive FSH stimulation is a key tool of assisted reproduction technology but can cause severe complications through the development of an excessive number of small ovarian follicles. We tested

the hypothesis that, in the late stages of ovulation induction, LH activity in the form of low-dose human CG (hCG) can stimulate and selectively modulate ovarian follicle function and growth, independently of FSH administration. Four groups of GnRH agonist-suppressed normoovulatory women (10 each group) received recombinant human FSH (r-hFSH) (150 IU/d) for 7 d followed by: group A, r-hFSH 150 IU/d alone; group B, r-hFSH 50 IU/d and hCG 50 IU/d; group C, r-hFSH 25 IU/d and hCG 100 IU/d; group D, hCG 200 IU/d alone. Despite several days of lowered or absent r-hFSH administration, 70% of hCG-treated patients successfully completed treatment. In these subjects, preovulatory E2 levels and large (>14 mm diameter) ovarian follicle development were not reduced; conversely, the number of small (<10 mm diameter) ovarian follicles was significantly decreased in groups B-D vs. group A. Low-dose hCG administration did not cause follicle luteinization. We conclude that, following FSH priming, LH activity administration can: 1) stimulate folliculogenesis for several days, in spite of rapidly declining FSH levels; and 2) hasten small follicle demise. Therefore, LH activity administration could be used to design radically novel ovulation induction regimens that, by partly or completely replacing mid-/late follicular phase FSH administration, may reduce costs and improve safety of assisted reproduction technology.

15/3,AB/51
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14380732 PMID: 11741284
Follistatin inhibits the function of the oocyte-derived factor BMP-15.
Otsuka F; Moore RK; Iemura S; Ueno N; Shimasaki S
Department of Reproductive Medicine, University of California San Diego, School of Medicine, 9500 Gilman Drive, La Jolla, California 92093-0633, USA.
Biochemical and biophysical research communications (United States) Dec 21 2001, 289 (5) p961-6, ISSN 0006-291X--Print Journal Code: 0372516
Contract/Grant No.: F32 HD41320-01; HD; United States NICHD; T32 HD07203-17; HD; United States NICHD; U54HD12303; HD; United States NICHD
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Recent studies have highlighted the importance of a novel oocyte-derived growth factor, bone morphogenetic protein-15 (BMP-15) in the regulation of proliferation and differentiation of granulosa cells in the ovary. Namely, BMP-15 stimulates granulosa cell mitosis and inhibits follicle-stimulating hormone (FSH) receptor mRNA expression in granulosa cell, thereby playing a critical role in the elaborate mechanism controlling ovarian folliculogenesis. At present, however, nothing is known about molecules which may regulate the biological activity of BMP-15. Here we demonstrate evidence that follistatin can form an inactive complex with BMP-15, through which follistatin inhibits BMP-15 bioactivities. The binding of follistatin to BMP-15 was directly demonstrated by a surface plasmon resonance biosensor, and the ability of follistatin to inhibit BMP-15 functions was determined by established BMP-15 bioassays using primary rat granulosa cells. Specifically, follistatin attenuated BMP-15 stimulation of granulosa cell proliferation and reversed BMP-15 inhibition of FSH receptor mRNA expression leading to the suppression of FSH-induced progesterone synthesis. This is the first demonstration of biochemical interaction and biological antagonism of follistatin and BMP-15, which may be involved in the complex yet well-controlled mechanism of the regulation of follicle growth and development.

15/3,AB/52
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14333153 PMID: 11704115
The physiology of folliculogenesis: the role of novel growth factors.
Erickson GF; Shimasaki S
Department of Reproductive Medicine, School of Medicine, University of California, San Diego, La Jolla, California 92093-0674, USA. gerickson@ucsd.edu
Fertility and sterility (United States) Nov 2001, 76 (5) p943-9, ISSN 0015-0282--Print Journal Code: 0372772
Contract/Grant No.: U54 HD12303; HD; United States NICHD
Publishing Model Print
Document type: Journal Article; Research Support, U.S. Gov't, P.H.S.; Review

Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: To assess major physiological events underlying follicul genesis, including FSH-dependent dominant follicle (DF) formation, LH/hCG signaling, and the role of novel regulatory molecules in these developmental processes. DESIGN: Review of some of the past and recent advances in ovarian biology, focusing attention on [1] two novel oocyte-derived growth factors, growth differentiation factor-9 (GDF-9) and bone morphogenetic protein (BMP-15); and [2] a recently discovered follicular insulin-like growth factor binding protein-4 (IGFBP-4) protease, pregnancy-associated plasma protein-A (PAPP-A), that can degrade the FSH antagonist IGFBP-4. RESULT(S): Oocyte-derived GDF-9 and BMP-15 are obligatory for follicul genesis and female fertility in laboratory animals through their ability to stimulate granulosa cell proliferation and modulate FSH-dependent cytodifferentiation. The expression of these growth factors in human primary oocytes supports the hypothesis that GDF-9 and BMP-15 could be involved in ovary function in women. Pregnancy-associated plasma protein-A is a marker for the human dominant follicle and its product the corpus luteum raising the possibility that this putative FSH antagonist might regulate FSH bioactivity during follicul genesis and luteogenesis. CONCLUSION(S): Oocyte-derived and granulosa-derived regulatory proteins perform very important functions in FSH-dependent follicul genesis. The current challenges are to understand the role of these novel proteins in ovary physiology and pathophysiology in women.

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14265388 PMID: 11566718
Effect of bone morphogenetic protein-7 on follicul genesis and ovulation in the rat.
Lee WS; Otsuka F; Moore RK; Shimasaki S
Department of Reproductive Medicine, University of California San Diego, School of Medicine, La Jolla, California 92093-0633, USA.
Biology of reproduction (United States) Oct 2001, 65 (4) p994-9, ISSN 0006-3363--Print Journal Code: 0207224
Contract/Grant No.: T32 HD07203-17; HD; United States NICHD; U54HD12303; HD; United States NICHD
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We have previously established the presence of a functional bone morphogenetic protein (BMP) system in the ovary by demonstrating the expression of BMP ligands and receptors as well as novel cellular functions. Specifically, BMP-4 and BMP-7 are expressed in theca cells, and their receptors by granulosa cells. These BMPs enhanced and attenuated the stimulatory action of FSH on estradiol and progesterone production, respectively. To investigate the underlying mechanism of the differential regulation, we analyzed mRNA levels for key regulators in the steroid biosynthetic pathways by RNase protection assay. BMP-7 enhanced P450 aromatase (P450arom) but suppressed steroidogenic acute regulatory protein (StAR) mRNAs induced by FSH, whereas mRNAs encoding further-downstream steroidogenic enzymes, including P450 side-chain cleavage enzyme and 3beta-hydroxysteroid dehydrogenase, were not significantly altered. These findings suggest that BMP-7 stimulation and inhibition of P450arom and StAR mRNA expression, respectively, may play a role in the mechanisms underlying the differential regulation of estradiol and progesterone production. To establish the physiological relevance of BMP functions, we investigated the in vivo effects of injections of recombinant BMP-7 into the ovarian bursa of rats. Ovaries treated with BMP-7 had decreased numbers of primordial follicles, yet had increased numbers of primary, preantral, and antral follicles, suggesting that BMP-7 may act to facilitate the transition of follicles from the primordial stage to the pool of primary, preantral, and antral follicles. In this regard, we have also found that BMP-7 caused an increase in DNA synthesis and proliferation of granulosa cells from small antral follicles in vitro. In contrast to the stimulatory activity, BMP-7 exhibited pronounced inhibitory effects on ovulation rate and serum progesterone levels. These findings establish important new biological activities of BMP-7 in the context of ovarian physiology, including follicul genesis and ovulation.

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14171503 PMID: 11451583

Production and actions of inhibin and activin during follicul ogenesis in the rat.
Findlay J K; Drummond A E; Dyson M; Baillie A J; Robertson D M; Ethier J F
Prince Henry's Institute of Medical Research, P.O. Box 5152, Vic. 3168, Clayton, Australia. jock.findlay@rd.monash.edu.au
Molecular and cellular endocrinology (Ireland) Jun 30 2001, 180 (1-2) p139-44 ISSN 0303-7207--Print Journal Code: 7500844
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Evidence to enhance the premise that inhibin and activin are local regulators of ovarian follicul ogenesis is presented in this review. Granulosa cells (GC) have been identified as the source of inhibin/activin in the ovary on the basis of mRNA and protein localisation and the measurement of the inhibin forms in GC conditioned media. Expression of the subunit mRNAs changed with follicular development, being maximal in the ovaries of 8-day-old rats, where secondary follicles predominate. The expression of beta subunit mRNAs by GC isolated from diethylstilboestrol (DES)-treated immature rats, was reduced in the absence of any change in alpha subunit mRNA expression. Dimeric inhibin-A, -B and free alpha subunit were produced by ovarian cell cultures prepared from 4- to 12-day-old rats. Inhibin-A production by these cultures was responsive to FSH and TGF-beta, with preantral follicles of day 8 ovaries exerting effects so profound that the inhibin A/alpha subunit ratio increased, most likely due to a stimulation of beta(A) subunit production. In contrast, inhibin-B was not stimulated by TGF-beta until day 8 and FSH until day 12. Fractionation of GC conditioned media revealed a prominence of free alpha subunit and inhibin-A, but little inhibin-B, suggesting that inhibin-B production declines with follicular development. Activin receptor types I and II, betaglycan (beta-glycan) mRNAs were present in the rat ovary and showed distinct patterns of expression between postnatal days 4 and 12. Oocytes and GC localised activin receptor, Smad and beta-glycan proteins, with beta-glycan also present in theca cells (TC). These data indicate that activin/TGF-beta signalling machinery and factors which influence these pathways, are present in the postnatal rat ovary. Our hypothesis that inhibin and activin play important and changing autocrine/paracrine roles in the growth and differentiation of follicles, including the oocyte, has been supported by these studies.

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14093385 PMID: 11358118
Mechanism of GnRH receptor signaling on gonadotropin release and gene expression in pituitary gonadotrophs.
Shacham S; Harris D; Ben-Shlomo H; Cohen I; Bonfil D; Przedecki F; Lewy H; Ashkenazi I E; Seger R; Naor Z
Department of Biochemistry, George S. Wise Faculty of Life Sciences, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel.
Vitamins and hormones (United States) 2001, 63 p63-90, ISSN 0083-6729--Print Journal Code: 0413601
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Gonadotropin releasing hormone (GnRH), the first key hormone of reproduction, is synthesized and secreted from the hypothalamus in a pulsatile manner and stimulates pituitary gonadotrophs (5-10% of the pituitary cells) to synthesize and release gonadotropin luteinizing hormone (LH) and follicle stimulating hormone (FSH). Gonadotrophs consist of 60% multihormonal cells (LH+FSH) and 18% LH- and 22% FSH-containing cells. LH and FSH, members of the glycoprotein hormone family, stimulate spermatogenesis, follicul ogenesis, and ovulation. Although GnRH plays a pivotal role in gonadotropin synthesis and release, other factors such as gonadal steroids and gonadal peptides exert positive and negative feedback mechanisms, which affect GnRH actions. GnRH actions include activation of phosphoinositide turnover as well as phospholipase D and A2, mobilization and influx of Ca2+, activation of protein kinase C (PKC) and mitogen-activated protein kinase (MAPK). A complex crosstalk between the above messenger molecules mediates the diverse actions of GnRH. Understanding the signaling mechanisms involved in GnRH actions is the basis for our understanding of basic reproductive functions in general and gonadotropin synthesis and release in particular.

15/3,AB/56
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14004662 PMID: 11232021
Luteinizing hormone activity in menotropins optimizes follicul ogenesis and treatment in controlled ovarian stimulation.
Filicori M, Cognigni G E, Taraborrelli S, Spettoli D, Ciampaglia W, Tabarelli De Fatis C, Pocognoli P, Cantelli B, Boschi S
Reproductive Endocrinology Center, Department of Internal Medicine, University of Bologna, 40138 Bologna, Italy. filicori@med.unibo.it
Journal of clinical endocrinology and metabolism (United States) Jan 2001, 86 (1) p337-43, ISSN 0021-972X--Print Journal Code: 0375362
Publishing Model: Print
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Although the role that LH plays in folliculogenesis is still controversial, recent evidence points toward facilitatory actions of LH activity in ovulation induction. Thus, we compared the response to either highly purified FSH (75 IU FSH/ampoule; group A, 25 subjects) or human menopausal gonadotropin (75 IU FSH and 75 IU LH /ampoule; group B, 25 subjects) in normoovulatory GnRH agonist-suppressed women, candidates for intrauterine insemination. A fixed regimen of 2 daily ampoules of highly purified FSH or human menopausal gonadotropin was administered in the initial 14 days of treatment; menotropin dose adjustments were allowed thereafter. Treatment was monitored with daily blood samples for the measurement of LH, FSH, 17beta-estradiol (E(2)), progesterone, testosterone, hCG, inhibin A, and inhibin B, and transvaginal pelvic ultrasound was performed at 2-day intervals. Although preovulatory E(2) levels were similar, both the duration of treatment (16.1 +/- 0.8 vs. 12.6 +/- 0.5 days; P< 0.005) and the per cycle menotropin dose (33.6 +/- 2.4 vs. 23.6 +/- 1.1 ampoules; P < 0.005) were lower in group B. In the initial 14 treatment days the area under the curve of FSH, progesterone, testosterone, inhibin A, and inhibin B did not differ between the 2 groups, whereas LH, hCG, and E(2) areas under the curve were higher in group B. The occurrence of small follicles (<10 mm) and the inhibin B/A ratio in the late follicular phase were significantly reduced in group B. A nonsignificant trend toward a higher multiple gestation rate was present in group A (60% vs. 17%). We conclude that ovulation induction with LH activity-containing menotropins is associated with 1) shorter treatment duration, 2) lower menotropin consumption, and 3) reduced development of small ovarian follicles. These features can be exploited to develop regimens that optimize treatment outcome, lower costs, and reduce occurrence of complications such as multiple gestation and ovarian hyperstimulation.

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13964856 PMID: 11217062
Dynamic changes in plasma concentrations of gonadotropins, inhibin, estradiol-17beta and progesterone in cows with ultrasound-guided follicular aspiration.
Tohei A, Shi F X, Ozawa M, Ima K, Takahashi H, Shimohira I, Kojima T, Watanabe G, Taya K
Laboratory of Veterinary Physiology, Tokyo University of Agriculture and Technology, Fuchu, Japan.
Journal of veterinary medical science / the Japanese Society of Veterinary Science (Japan) Jan 2001, 63 (1) p45-50, ISSN 0916-7250--Print Journal Code: 9105360
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
To elucidate the effects of ultrasound-guided transvaginal follicular aspiration, plasma concentrations of FSH, LH, inhibin, estradiol-17beta and progesterone, and folliculogenesis were examined in Holstein cows. Four clinically healthy cows with regular estrous cycles were scanned by ultrasound per rectum once a week for 9 weeks before the commencement of follicular aspiration. All visible follicles were divided into 3 categories based on their sizes (2 < or = small < 5 mm; 5 < or = medium < 10 mm; large > or = 10 mm). The follicular aspiration was started at random during the estrous cycle and conducted under epidural anesthesia induced with 5 ml of 2%-lidocaine once a week for 6 weeks. The average number of total visible follicles > or = 2 mm in diameter at 7 days after aspiration (21.7 +/- 7.4, n = 24) was similar to that before starting aspiration (26.7 +/- 10.5, n = 36). Plasma inhibin and estradiol-17beta declined and fell to a trough on 1.5 days and returned to pre-aspiration values by 5 days after aspiration. Plasma concentrations of FSH increased and reached peak levels between 1 and 1.5 days after aspirations.

Plasma concentrations of LH also increased and reached peak levels between 0.5 and 1.5 days after aspirations. Both plasma FSH and LH had returned to pre-aspiration levels by 5 days after aspirations. Plasma concentrations of progesterone did not change with the follicular aspiration. These results demonstrate that follicular aspiration decreases plasma concentrations of inhibin and estradiol-17beta, which in turn leads to a rise in plasma concentrations of FSH and LH. It is suggested that marked increases in plasma concentrations of FSH and LH after the aspiration stimulate the development and maturation of a new cohort of follicles within one week in cows.

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13875993 PMID: 10927623
Temporal and hormonal regulation of inhibin protein and subunit mRNA expression by post-natal and immature rat ovaries.
Drummond A E; Dyson M; Thean E; Groome N P; Robertson D M; Findlay J K
Prince Henry's Institute of Medical Research, PO Box 5152, Clayton, Victoria 3168, Australia. ann.drummond@med.monash.edu.au
Journal of endocrinology (England) Aug 2000, 166 (2) p339-54, ISSN 0022-0795--Print Journal Code: 0375363
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The contribution of specific follicle populations to dimeric inhibin production and inhibin subunit mRNA expression by the rat ovary has been investigated in two model systems, granulosa cells isolated from 25-day-old diethylstilboestrol (DES)-treated rats and post-natal rat ovaries, dispersed in culture or whole ovaries, using specific two-site immunoassays and 'real time' PCR. Media from FSH-stimulated granulosa cell cultures fractionated by gel filtration and RP-high performance liquid chromatography revealed two predominant peaks of alpha subunit activity which were attributed to alpha subunit and 31 k dimeric inhibin-A. The corresponding inhibin-B levels were low. FSH stimulation did not alter the ratio of inhibin-A:alpha subunit produced by granulosa cells. All three inhibin subunit mRNAs were expressed by granulosa cells, with eight-fold more alpha subunit mRNA relative to either of the beta subunits. Administration of DES to immature rats prior to the isolation of granulosa cells from the ovary led to beta(A) and beta(B) mRNA expression being down-regulated in the absence of any significant change in alpha subunit expression by the granulosa cells. Inhibin-A, -B and -alpha subunit were produced by basal and stimulated cultures of ovarian cells prepared from 4-, 8- and 12-day-old rats, indicating that primary, preantral and antral follicles contribute to total inhibin production. Consistent with these results, follicles within these ovaries expressed all three inhibin subunit mRNAs, with maximal expression observed in the ovaries of 8-day-old rats. The appearance of antral follicles in the ovary at day 12 led to a decline in the mRNA levels of each of the subunits but was most evident for the beta subunits. There was a profound influence of secondary preantral follicles on dimeric inhibin-A production, with FSH stimulation increasing inhibin-A relative to alpha subunit levels in cultures of ovarian cells prepared from 8-day-old rats. Thus, preantral follicles exposed to FSH contribute significantly to beta(A) subunit production by the ovary. In contrast, primary and preantral follicles did not produce inhibin-B in response to FSH stimulation. Transforming growth factor-beta (TGF-beta) enhanced, in a time-dependent manner, the production of the inhibin forms by ovarian cells in culture, although inhibin-B production was not responsive until day 8. The simultaneous treatment of ovarian cell cultures with FSH and TGF-beta elicited the greatest increases in production of all the inhibin forms. In summary, ovaries of 4-, 8- and 12-day-old rats expressed inhibin subunit mRNAs and produced dimeric inhibin-A and -B and free alpha subunit. Preantral follicles (day-8 ovarian cell cultures) were particularly sensitive to stimulation by FSH and TGF-beta and had a substantial capacity for inhibin production. The production of oestrogen by follicles may be instrumental in regulating inhibin production given that beta subunit mRNA expression was down-regulated by DES. The mechanisms by which inhibin-A and inhibin-B are individually regulated are likely to be similar during the post-natal period, when folliculogenesis is being established, and diverge thereafter, when inhibin-A becomes the predominant form in the fully differentiated ovary.

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13835445 PMID: 10998422
Bone morphogenetic protein-15. Identification of target cells and biological functions.

Otsuka F; Yao Z; Lee T; Yamamoto S; Erickson G F; Shimasaki S
Department of Reproductive Medicine, University of California, San Diego, School of Medicine, La Jolla, California 92093-0633, USA.
Journal of biological chemistry (UNITED STATES) Dec 15 2000, 275 (50) p39523-8, ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: U54HD12303; HD; United States NICHD
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
In developing ovarian follicles, the regulation of cell proliferation and differentiation is tightly coordinated. Precisely how this coordination is achieved is unknown, but recent observations have suggested that molecules emitted by the oocyte are involved in the process. The newly discovered oocyte-specific growth factor, bone morphogenetic protein-15 (BMP-15), is one such molecule. At present, nothing is known about the target cells and biological functions of BMP-15. To fill this gap in our knowledge, recombinant BMP-15 and its antibody were produced and used to determine BMP-15 expression and bioactivity. BMP-15 mRNA and protein were shown to be co-expressed in oocytes throughout folliculogenesis, supporting the idea that BMP-15 is a physiological regulator of follicle cell proliferation and/or differentiation. To test this, we used primary cultures of rat granulosa cells (GCs). We found that BMP-15 is a potent stimulator of GC proliferation, and importantly, the mitogenic effect was follicle-stimulating hormone (FSH)-independent. By contrast, BMP-15 alone had no effect on steroidogenesis. However, it produced a marked decrease in FSH-induced progesterone production, but had no effect on FSH-stimulated estradiol production. This result indicates that BMP-15 is a selective modulator of FSH action. In summary, this study identifies GCs as the first target cells for BMP-15. Moreover, it identifies the stimulation of GC proliferation and the differential regulation of two crucial steroid hormones as the first biological functions of BMP-15. Significantly, BMP-15 is the first growth factor that can coordinate GC proliferation and differentiation in a way that reflects normal physiology.

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13791825 PMID: 11058434
The Parkes lecture: controlled ovarian stimulation in women.
Hillier S G
Reproductive Medicine Laboratory, Department of Reproductive and Developmental Sciences, University of Edinburgh Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH3 9EW, UK.
Journal of reproduction and fertility (ENGLAND) Nov 2000, 120 (2) p201-10, ISSN 0022-4251--Print Journal Code: 0376367
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Recent advances in knowledge of the endocrine and paracrine mechanisms that regulate human ovarian folliculogenesis have been paralleled by the introduction into clinical practice of new drugs that can be used safely and effectively to stimulate ovarian function in infertile women. Most notably, recombinant DNA technology has been applied to the production of molecularly pure forms of the gonadotrophins, FSH and LH, opening the way to the development of improved strategies for manipulating the ovarian paracrine system. The clinical objectives of controlled ovarian stimulation fall into two categories, depending on patient needs: (1) induction of multiple follicles from which mature oocytes can be harvested for use in assisted reproduction protocols such as in vitro fertilization and embryo transfer; or (2) induction of spontaneous ovulation of a single mature follicle so that conception might occur in vivo. This review summarizes the physiological principles upon which the use of gonadotrophins for clinical purposes is based, highlighting new opportunities for improved treatment as a result of the availability of recombinant FSH and LH.

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13789941 PMID: 11056116
The role of LH in ovarian stimulation: exogenous LH: let's design the future.
Levy D P; Navarro J M; Schattman G L; Davis O K; Rosenwaks Z
The Center For Reproductive Medicine and Infertility, Weill Medical College of Cornell University, New York, NY, USA.

Human reproduction (Oxford, England) (ENGLAND) Nov 2000, 15 (11) p2258-65, ISSN 0268-1161--Print Journal Code: 8701199
Publishing Model: Print; Comment in Hum Reprod. 2001 Apr;16(4) 803-5; Comment in PMID 11278238; Erratum in Hum Reprod 2001 Mar;16(3):598
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Historically, follicular stimulation protocols have included both FSH and LH in an attempt to mimic the physiology of normal human folliculogenesis. However, many recent gonadotrophin administration regimens have completely eliminated LH bioactivity. The importance and the amount of LH necessary for optimal follicular stimulation has been a topic of debate. Several recent studies have added to our understanding of the actions of androgens, oestrogens, gonadotrophins, and insulin on the follicle-oocyte unit, allowing a less speculative approach. Moreover, the availability of human gonadotrophins synthesized by recombinant DNA technology and gonadotrophin-releasing hormone (GnRH) antagonists, should soon permit a precise in-vivo assessment and re-evaluation of the historical 2-cell, two-gonadotrophin hypothesis. These pharmacological tools may also provide essential insights into the physiological roles of FSH and LH in human follicular development and oocyte maturation. The recombinant gonadotrophins give clinicians the unique opportunity to tailor ovarian stimulation regimens according to the patient's medical history, in an effort both to maximize oocyte yield and to improve oocyte quality.

15/3,AB/62
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13649154 PMID: 10889840
The pathophysiology of endometriosis-associated infertility: follicular environment and embryo quality.
Pellicer A; Albert C; Garrido N; Navarro J; Remohi J; Simon C
Instituto Valenciano de Infertilidad, Valencia University School of Medicine, Spain.
Journal of reproduction and fertility. Supplement (ENGLAND) 2000 , 55 p109-19, ISSN 0449-3087--Print Journal Code: 0225652
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Several retrospective analyses of IVF and oocyte donation programmes, performed to gain clinical knowledge of the factors implicated in the aetiology of endometriosis-associated infertility, have demonstrated that the quality of the embryo is affected in patients with endometriosis. To understand the mechanisms of this alteration, the endocrine, paracrine and autocrine conditions induced during folliculogenesis in women with and without endometriosis were investigated. The first approach was to study ovarian steroid secretion in women undergoing IVF. Progesterone concentrations in follicular fluid increased with the severity of the disease and an increase in progesterone accumulation in vitro was observed in basal and hCG-stimulated granulosa cell cultures. It is proposed that the pattern of progesterone secretion may be related to changes in the release of cytokines by ovarian and white blood cells. Hence, a second trial measured interleukin 1 (IL-1), IL-6 and vascular endothelial growth factor (VEGF) concentrations in serum, follicular fluid and granulosa cell cultures. IL-6 concentrations in serum were higher in the natural cycles of women with endometriosis than in women in the control group, and were modulated by ovarian stimulation, decreasing significantly in serum from stimulated cycles. In addition, IL-6 concentrations were higher in the follicular fluid of women with endometriosis than in those in the control group and IL-6 was released in higher amounts by granulosa luteal cells of patients with endometriosis. VEGF was accumulated in lower concentrations in the follicular fluid of patients with endometriosis. These observations indicate that infertility in patients with endometriosis may be related to alterations within the follicle which, in turn, result in oocytes and embryos of lower quality, as demonstrated in the IVF programme. In addition, these embryos have a reduced ability to implant, as observed in the oocyte donation model. These alterations may be induced by functional changes in the process of folliculogenesis that affect steroid synthesis, as well as by cytokine release by ovarian and blood cells.

15/3,AB/63
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13602299 PMID: 10831560
A prospective, randomized, controlled, double-blind, double-dummy comparison of recombinant and urinary HCG for inducing oocyte maturation and follicular luteinization in ovarian stimulation.

Driscoll G L; Tyler J P; Hangan J T; Fisher P R; Birdsall M A; Knight D C
City West IVF, Westmead, NSW, Australia.
Human reproduction (Oxford, England) (ENGLAND) Jun 2000, 15 (6)
p1305-10. ISSN:0268-1161--Print Journal Code: 8701199
Publishing Model: Print
Document type: Clinical Trial; Comparative Study; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
A randomized, controlled, double-blind, double-dummy, phase III clinical trial was conducted in 84 women to compare the efficacy of a.s.c. injection of 250 microg recombinant human chorionic gonadotrophin (rHCG; Ovidrel) to an i.m injection of 5000 IU urinary HCG (uHCG; Profasi) in inducing folliculogenesis, resumption of oocyte meiosis and luteinization after ovulation induction with recombinant follicle-stimulating hormone (Gonal-F). The study primary endpoint was comparison of the number of oocytes retrieved per patient receiving either compound. Secondary comparisons included the number of oocytes retrieved per follicles aspirated; the number of mature oocytes; normally fertilized oocytes; and cleaved embryos. There were no statistically significant differences between groups for the primary endpoint (mean +/- SD oocytes retrieved 10.8 +/- 4.5 for rHCG versus 10.3 +/- 5.1 for uHCG) or each of the secondary endpoints except for increased concentrations of progesterone 6-7 days after rHCG administration (353.2 +/- 215.1 versus 234.1 +/- 129.4 nmol/l; P < 0.004) and for HCG during the luteal phase following rHCG (P < 0.02). There were also no significant side-effects for either drug. Since the confidence intervals for the difference of the number of oocytes retrieved between the two treatment groups were within the bounds defined by the multi-trial protocol equivalence between rHCG and uHCG could be declared.

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13602281 PMID: 10831542
Embryo implantation and GnRH antagonists: embryo implantation: the Rubicon for GnRH antagonists.
Hernandez E R
Clinica de Reproduccion Asistida FIV-Madrid and Instituto de Bioquimica (CSIC-UCM), C/Alvarez de Baena 4, 28006 Madrid, Spain. ehernandezm@redit ex.es
Human reproduction (Oxford, England) (ENGLAND) Jun 2000, 15 (6)
p1211-6, ISSN:0268-1161--Print Journal Code: 8701199
Publishing Model: Print; Comment in Hum Reprod. 2000 Sep;15(9):1881-2; Comment in PMID: 10966978; Comment in Hum Reprod. 2000 Sep;15(9):1882-3; Comment in PMID: 10966979; Comment in Hum Reprod. 2001 Jun;16(6):1305-6; Comment in PMID: 11387310; Comment in Hum Reprod. 2001 Oct;16(10):2247; Comment in PMID: 11574529
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
When gonadotrophin-releasing hormone (GnRH) was discovered, the agonist and antagonist of GnRH were developed to control the release of FSH and LH by the gonadotrophs. More than 10 years of research were needed to develop a GnRH antagonist free of histamine release. Recent studies have shown that these GnRH antagonists are effective in preventing a rise in LH during ovarian stimulation in IVF. However, a decrease in ongoing pregnancies seems to suggest that implantation rates per transferred embryo are reduced in GnRH antagonist-stimulated cycles. In my opinion, these data highlight an area less well known to clinicians: the role of the GnRH antagonist at the cellular level in extrapituitary tissues. There are sufficient data in the literature suggesting that GnRH antagonist is an inhibitor of the cell cycle by decreasing the synthesis of growth factors. Given that, for folliculogenesis, blastomere formation and endometrium development, mitosis is everything; the interaction between the GnRH antagonist and the GnRH receptor (present in all these cells and tissues) may compromise the mitotic programme of these cells. This is the Rubicon for the GnRH antagonist: to demonstrate irrevocably that, at the minimal doses necessary to suppress LH release, it does not affect processes such as implantation, embryo development and folliculogenesis.

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13585574 PMID: 10813099
Inhibition of gonadotropin surge by a brief mid-cycle regimen of ethinyl estradiol and norethindrone: possible role in in vitro fertilization.
Letterie G S

Center for Reproductive Endocrinology and Fertility, Virginia Mason Medical Center, Seattle, Washington 98111, USA.
Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology (ENGLAND) Feb 2000, 14 (1) p1-4, ISSN 0951-3590--Print Journal Code: 8807913
Publishing Model Print
Document type: Clinical Trial; Comparative Study; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Various methods to prevent premature luteinizing hormone (LH) surge and improve cycle control during hyperstimulation for in vitro fertilization (IVF) are standard of care. The purpose of the present study was to determine the influence of a 5-day regimen of ethinyl estradiol (EE) and norethindrone (NET) on follicul genesis, gonadotropin surge, and ovulation. In a prospective randomized and comparative study, ten patients were assigned to two groups. A combination of 50 micrograms of EE and 1 mg of NET was used in groups I and II from days 6 through 10, and days 8 through 12, respectively. Blood samples and transvaginal ultrasound imaging were carried out throughout a 28-day cycle. Follicular diameter, plasma levels of LH, follicle-stimulating hormone (FSH), estradiol and progesterone, and endometrial thickness were determined. No LH surge or ovulation was detected in any patient studied. Peak estradiol concentrations were not significantly different between the groups (152.04 +/- 107.1 pg/ml vs 162.1 +/- 56.1 pg/ml [mean +/- SD] for groups I and II, respectively). No differences were noted between the groups for serum concentrations of FSH (range: 2-9 mIU/ml) or LH (range: 2-10 mIU/ml) for any given cycle day. Mean follicular diameters were not different between groups I and II (20.5 +/- 8.1 mm2 vs 20.6 +/- 14.2 mm2). Ultrasound assessment of mid-cycle follicular growth revealed diameters ranging from 18.5 mm2 to 34.0 mm2. Endometrial thickness ranged from 8 to 10 mm. There was no evidence of ovulation on ultrasound examination and either persistence or gradual resolution of follicles through the luteal phase. Peak serum concentrations at mid-luteal phase were < or = 2 ng/ml. In this pilot study, the combination of EE and NET restricted to a 5-day course beginning on day 6 or 8 permitted follicul genesis but effectively inhibited mid cycle LH surge and ovulation. Such regimens may have a role in IVF cycles for prevention of premature LH surges, especially as stimulation regimens evolve toward decreased gonadotropin use for stimulation and strict FSH preparations with the potential need for less complete pituitary suppression.

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13393371 PMID: 10469685
A prospective, randomized comparison of ovulation induction using highly purified follicle-stimulating hormone alone and with recombinant human luteinizing hormone in in-vitro fertilization.
Sills E S; Levy D P; Moomjy M; McGee M; Rosenwaks Z
Center for Reproductive Medicine and Infertility, Department of Obstetrics & Gynecology, The New York Presbyterian Hospital-Cornell Medical Center and General Clinical Research Center, Rockefeller University, New York, New York, USA.
Human reproduction (Oxford, England) (ENGLAND) Sep 1999, 14 (9) p2230-5, ISSN 0268-1161--Print Journal Code: 8701199
Publishing Model Print
Document type: Clinical Trial; Comparative Study; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The commercial availability of highly purified, s.c. administered urinary follicle stimulating hormone (FSH) preparations for ovarian stimulation marked the beginning of a new era in the treatment of infertility. As these new formulations contain essentially no luteinizing hormone (LH), supplemental LH may be needed for optimal follicul genesis. It was the aim of this pilot study to compare fertilization rates, embryo morphology, implantation rates and pregnancy outcomes prospectively in two age-matched patient groups: women who received highly purified FSH (FSH-HP) (n = 17), and women who received FSH-HP plus recombinant human LH (rhLH, n = 14) throughout ovarian stimulation. All patients received mid-luteal pituitary down-regulation with s.c. gonadotrophin-releasing hormone agonist (GnRHa) (leuprolide). Mean implantation rates were 26.9 and 11.9% in the FSH-HP only and FSH-HP + rhLH groups respectively. The mean clinical pregnancy/initiated cycle rate was 64.7 and 35.7% for the FSH-HP only and FSH-HP + rhLH patients respectively. FSH-HP patients and FSH-HP + rhLH patients achieved clinical pregnancy/transfer rates of 68.8 and 45.5% respectively. One patient in the FSH-HP + rhLH group had a spontaneous abortion; no pregnancy losses occurred in the FSH-HP only group. There were more cancellations for

poor ovarian response among FSH-HP + rhLH patients (n = 3) than among FSH-HP patients (n = 1). The trend toward better pregnancy outcomes among patients who received FSH-HP without supplemental rhLH did not reach statistical significance. It is postulated that appropriate endogenous LH concentrations exist despite luteal GnRHa pituitary suppression, thereby obviating the need for supplemental LH administration.

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13365856 PMID: 10443656
Luteinizing hormone activity supplementation enhances follicle-stimulating hormone efficacy and improves ovulation induction outcome.
Filicori M; Cognigni G E; Taraborrelli S; Spettoli D; Ciampaglia W; de Fatis C T; Pocognoli P
Reproductive Endocrinology Center, University of Bologna, Italy. filicori@med.unibo.it
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Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Although FSH is essential to stimulate ovarian folliculogenesis, increasing physiological and clinical evidence suggests that moderate LH stimulation may also be critical for optimal follicle and oocyte development. Conversely, a clinical trend exists toward conducting controlled ovarian hyperstimulation (COH) in a LH-depleted environment, as recently developed gonadotropin preparations are devoid of LH activity, and endogenous LH is suppressed with GnRH analogs in most COH cycles. To investigate the role of LH activity during COH we supplemented highly purified (HP) FSH with low dose hCG in GnRH agonist-suppressed women. Twenty normoovulatory women were pretreated with a GnRH agonist and after 2 weeks were randomly assigned to receive HP FSH (150 IU/day) alone (group A; 10 patients) or combined with hCG (50 IU/day; group B; 10 patients). The HP FSH dose was increased after 14 days only in cases of inadequate response. Treatment was monitored with pelvic ultrasound and daily hormone determinations. None of the patients of group B and 8 of group A required more than 14 days of treatment and increments of the FSH dose. Folliculogenesis and 17beta-estradiol (E2) secretion progressed more rapidly and evenly in group B. Although preovulatory follicle number and E2 concentrations were comparable, patients in group B required a shorter stimulation time (12.5+/-0.6 vs. 17.3+/-0.7 days in group A; P < 0.0001) and a lower HP FSH dose (1725+/-84 vs. 2670+/-164 IU in group A; P < 0.0001). Serum levels of LH, E2, progesterone, and testosterone did not differ between the 2 groups; serum FSH was higher in group A. We conclude that LH activity promotes folliculogenesis in synergy with FSH in the mid- to late follicular phase and that low dose hCG coadministration optimizes COH by 1) enhancing FSH action, 2) accelerating ovarian follicle development, 3) shortening COH duration, 4) lowering HP FSH requirements, and 5) reducing COH cost. Thus, moderate LH activity in the follicular phase plays a positive physiological and clinical role in folliculogenesis and ovulation induction.

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13325194 PMID: 10399054
Recombinant luteinizing hormone in ovarian hyperstimulation after stimulation failure in normogonadotropic women.
Lantt T; Cohrca A; Fischl F; Huber J C
Division of Gynecology, University of Vienna Medical School, Austria.
Gynecological endocrinology - the official journal of the International Society of Gynecological Endocrinology (ENGLAND) Apr 1999, 13 (2) p98-103, ISSN 0951-3590--Print Journal Code: 8807913
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The aim of this study was to examine the effect of an additional administration of recombinant luteinizing hormone (r-LH) to a gonadotropin-releasing hormone agonist (GnRHa) long protocol using recombinant follicle-stimulating hormone (r-FSH). In particular we determined whether such a stimulation protocol would be more

effective in women (1) who respond poorly to stimulation with GnRHa long protocol using r-FSH only, and (2) whose LH concentrations after down-regulation in the cancelled cycle were low but above the values reported in the literature to be sufficient for folliculogenesis. After GnRHa desensitization 150 IU r-FSH and 75 IU r-LH were administered subcutaneously daily to six normogonadotropic women with low response to ovarian hyperstimulation using a GnRHa long protocol with r-FSH and low LH concentrations after down-regulation in the cancelled cycle. All six women had an oocyte retrieval and an embryo transfer after follicular stimulation. One women conceived but had a miscarriage in the eleventh week of gestation. Our results suggest that women with low response to a GnRHa long protocol with r-FSH and whose LH concentration after down-regulation in the cancelled cycles were low, benefit from the additional administration of r-LH in a GnRHa long protocol using r-FSH. It seems that due to the additional administration of r-LH the LH concentration in the follicular phase is sufficient to support folliculogenesis.

15/3,AB/69
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13234282 PMID: 10210289
The effect of follicle-stimulating hormone (FSH) on the expression of FSH receptor in cultured rat granulosa cells.
Tano M; Minegishi T; Kishi H; Kameda T; Abe Y; Miyamoto K
Department of Obstetrics and Gynecology School of Medicine, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi, Japan.
Life sciences (ENGLAND) 1999, 64 (12) p1063-9, ISSN 0024-3205--Print Journal Code: 0375521
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The acquisition of FSH receptors during folliculogenesis is believed to be a key event in the subsequent development of the follicle. The regulation by FSH of FSH receptor expression and function were further studied using cultured granulosa cells of diethylstilbestrol (DES)-primed immature rats. Incubation of rat granulosa cells with FSH led to a reduction in FSH receptor levels for a short time (6 h), followed by an increase in FSH receptor levels that reached maximum of around 150% of the initial level within 3 days after the addition of FSH. FSH stimulation caused a reduced cAMP response to subsequent FSH treatment and a time course experiment demonstrated that this response was detectable within 30 min of exposure to FSH and reached a plateau after 4 h to 24 h. The recovery of FSH responsiveness in cAMP production of granulosa cells was seen after 48 h of FSH-free interval. Treatment with forskolin (FSK) enhanced the effect of subsequent FSH on the production of intracellular cAMP. Treatment with PMA did not affect the response to subsequent FSH treatment. These data showed that the FSH is essential for the suppression of the FSH receptor function in the adenylyl cyclase pathway. Desensitization of cellular response to continuous agonist stimulation may occur because of changes in the numbers of FSH receptor, as well as changes in the functional properties of the effector system

15/3,AB/70
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13150519 PMID: 9886804
Activin from secondary follicles causes small preantral follicles to remain dormant at the resting stage.
Mizunuma H; Liu X; Andoh K; Abe Y; Kobayashi J; Yamada K; Yokota H; Ibuki Y; Hasegawa Y
Department of Obstetrics and Gynecology, Gunma University School of Medicine, Maebashi, Japan. mizunuma@hews.sb.gunma-u.ac.jp
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Publishing Model: Print
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Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The purpose of the present study was to investigate 1) whether activin A can cause primary follicles to become dormant at the resting stage, and 2) the role of the secondary follicle on follicular growth of primary follicles. Preantral follicles (100-120 micrometer in diameter) harvested from adult mice and cultured in in vitro follicle culture system showed a significant increase in size and estrogen and inhibin secretion in response to FSH, but the administration of activin A blocked the effect of

FSH. Withdrawal of activin A not only restored the follicular response to FSH but also enhanced the effect of FSH, indicating that the action of activin A is to cause small preantral follicles to become dormant at the preantral stage. To investigate the role of secondary follicles in early folliculogenesis, small preantral follicles were cocultured with secondary follicle (300-350 micrometer in diameter) in the presence of FSH. The secondary follicle showed a significant increase in follicular diameter as a result of stimulation by FSH, but the small preantral follicles did not increase in size. After removal of the secondary follicle, however, the small preantral follicles commenced follicular growth, indicating that the growth of small preantral follicles is suppressed by the secondary follicle. Administration of the activin binding protein follistatin caused a significant increase in follicular diameter of both small preantral and secondary follicles as a result of stimulation by FSH. These results have suggested that secondary follicles cause primary follicles to become dormant at the resting stage by secreting activin.